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42 CFR Part 11
Clinical Trials Registration and Results Information Submission; Final Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

42 CFR Part 11

[Docket Number NIH–2011–0003]

RIN 0925–AA55

Clinical Trials Registration and Results Information Submission

AGENCY: National Institutes of Health, Department of Health and Human Services.

ACTION: Final rule.

SUMMARY: This final rule details the requirements for submitting registration and summary results information, including adverse event information, for specified clinical trials of drug products (including biological products) and device products and for pediatric postmarket surveillances of a device product to *ClinicalTrials.gov*, the clinical trial registry and results data bank operated by the National Library of Medicine (NLM) of the National Institutes of Health (NIH). This rule provides for the expanded registry and results data bank specified in Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) to help patients find trials for which they might be eligible, enhance the design of clinical trials and prevent duplication of unsuccessful or unsafe trials, improve the evidence base that informs clinical care, increase the efficiency of drug and device development processes, improve clinical research practice, and build public trust in clinical research. The requirements apply to the responsible party (meaning the sponsor or designated principal investigator) for certain clinical trials of drug products (including biological products) and device products that are regulated by the Food and Drug Administration (FDA) and for pediatric postmarket surveillances of a device product that are ordered by FDA.

DATES: These regulations are effective on January 18, 2017. Additional information on the effective date and the compliance date can be found in Section IV.F.

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SUPPLEMENTARY INFORMATION:

Executive Summary

Purpose of This Regulatory Action

This final rule clarifies and expands requirements for the submission of clinical trial registration and results information to the *ClinicalTrials.gov* database, which is operated by the NLM. It implements the provisions of section 402(j) of the Public Health Service Act (PHS Act) (42 United States Code (U.S.C.) 282(j)) as amended by Title VIII of FDAAA and including technical corrections made to FDAAA under Public Law 110–316), which were intended to improve public access to information about certain clinical trials of U.S. FDA-regulated drugs, biological products, and devices (also referred to as ''FDA-regulated drugs, biological products, and devices'' in this preamble) and certain pediatric postmarket surveillances of a device. Under section 402(j) of the PHS Act, those responsible for specified clinical trials of these FDA-regulated products have been required to submit registration information to *ClinicalTrials.gov* since December 26, 2007, summary results information for clinical trials of approved products as of September 27, 2008, and certain adverse events information since September 27, 2009. Section 402(j) of the PHS Act requires the Secretary of Health and Human Services to use rulemaking to expand the requirements for submission of summary results information, and authorizes the Secretary to use rulemaking to make other changes that enhance, but do not decrease, the available information about the specified trials.

This final rule does not impose requirements on the design or conduct of clinical trials or on the data that must be collected during clinical trials. Instead it specifies how data that were collected and analyzed in accordance with a clinical trial's protocol are submitted to *ClinicalTrials.gov*. No patient-specific data are required to be submitted by this rule or by the law this rule is intended to implement.

The major provisions of this rule are summarized below. More detailed discussions of these provisions are in Sections III and IV of this preamble.

Summary of the Major Provisions of the Regulatory Action

Applicable Clinical Trial

This final rule clarifies which clinical trials of FDA-regulated drug products (including biological products) and device products and which pediatric postmarket surveillances of a device product, are applicable clinical trials for which information must be submitted to *ClinicalTrials.gov*. The final rule considers all interventional clinical trials with one or more arms and with one or more pre-specified outcome measures to be controlled clinical trials. The final rule does not consider any expanded access use (*e.g.,* access under treatment INDs or treatment protocols, which provide widespread access, access for intermediate-sized patient populations, or access for individual patients) to be an applicable clinical trial. The final rule also describes an approach for evaluating, prior to registration, whether a particular clinical trial or study is an applicable clinical trial (see Section IV.A.5 and Section IV.B.2).

Responsible Party

This final rule specifies that there must be one (and only one) responsible party for purposes of submitting information about an applicable clinical trial. The sponsor of an applicable clinical trial will be considered the responsible party, unless and until the sponsor designates a qualified principal investigator as the responsible party. This final rule specifies the approach for determining who will be considered the sponsor of an applicable clinical trial under various conditions, what qualifies a principal investigator to be designated a responsible party by a sponsor, and how responsibility reverts to the sponsor if a designated principal investigator is unable to fulfill the requirements for submitting information to *ClinicalTrials.gov* unless and until the sponsor designates another principal investigator as the responsible party (see Section IV.A.2).

Registration

This final rule specifies requirements for registering applicable clinical trials at *ClinicalTrials.gov*. It requires that the responsible party register an applicable clinical trial not later than 21 calendar days after enrolling the first human subject (also referred to as participant or subject), and it specifies the data elements of clinical trial information that must be submitted at the time of registration. These data elements include the descriptive information, recruitment information, location and contact information, and administrative data elements listed in section 402(j) of the PHS Act, as well as additional required data elements under the Secretary's authority to modify the registration information requirements by

rulemaking as long as such modifications improve, and do not reduce, the clinical trial information available to the public in *ClinicalTrials.gov*. We consider these additional required registration data elements necessary to enable the NIH to implement other statutory provisions, indicate the status of human subjects protection review of the trial, facilitate the public's ability to search and retrieve information from *ClinicalTrials.gov*, and help ensure that entries are meaningful and unambiguous. We note that some of these additional data elements required under this rule were included in *ClinicalTrials.gov* before FDAAA was enacted or have been implemented since 2007 as optional data elements (see Section IV.B).

Although section 402(j) of the PHS Act includes a provision delaying public posting of registration information for applicable clinical trials of unapproved or uncleared device products until the device product is approved or cleared, the final rule includes a provision under which the responsible party for an applicable device clinical trial can indicate to the Agency that it is authorizing the public posting of clinical trial registration information that would otherwise fall under the delayed posting provision prior to approval or clearance of the product (see Section IV.B.5).

Expanded Access Information

Section 402(j) of the PHS Act requires the submission of information regarding whether, for an applicable drug clinical trial of an unapproved drug product (including an unlicensed biological product), expanded access to the investigational product being studied in the applicable clinical trial is available under section 561 of the Federal Food, Drug, and Cosmetic Act (FD&C Act). If the responsible party for an applicable clinical trial of an unapproved drug product (including an unlicensed biological product) is both the sponsor of the applicable clinical trial being registered and the manufacturer of the unapproved product, this rule requires the submission of a separate expanded access record containing details about how to obtain access to the investigational product. Once an expanded access record has been created for a particular investigational product and a National Clinical Trial (NCT) number has been assigned to it, the responsible party must update the applicable clinical trial(s) with that NCT number and provide that NCT number when submitting clinical trial registration information for any future applicable clinical trial(s) studying the same investigational product. The NCT number for the expanded access record allows *ClinicalTrials.gov* to link the existing expanded access record to the study record for the clinical trial (see Section IV.B.5 and Section IV.D.3).

Results Information Submission

This final rule addresses the statutory requirement for the submission of summary results information for applicable clinical trials of drug products (including biological products) and device products that are approved, licensed, or cleared by FDA. It also extends the requirement for results information submission to applicable clinical trials of drug products (including biological products) and device products that are not approved, licensed, or cleared by FDA. The rule requires the submission of data in a tabular format summarizing participant flow; demographic and baseline characteristics; primary and secondary outcomes, as well as results of any scientifically appropriate statistical tests; and adverse event information. In addition, the rule requires the submission of the full protocol and statistical analysis plan (if a separate document) (see Section III.D).

In general, this rule requires the submission of results information not later than 1 year after the completion date (referred to as the ''primary completion date'') of the clinical trial, which is defined as the date of final data collection for the primary outcome measure. Results information submission could be delayed for up to 2 additional years from the date of submission of a certification that either an unapproved, unlicensed, or uncleared product studied in the trial is still under development by the manufacturer or that approval will be sought within 1 year after the primary completion date of the trial for a new use of an approved, licensed, or cleared product that is being studied in the trial. This rule also permits responsible parties to request extensions to the results information submission deadlines for ''good cause'' as well as a permanent waiver of results information submission requirements for extraordinary circumstances (see Section IV.C.3 and Section IV.C.6).

Adverse Events Information

This final rule requires the responsible party to submit information summarizing the number and frequency of adverse events experienced by participants enrolled in a clinical trial, by arm or comparison group, as well as a brief description of each arm or group as a component of clinical trial results information. It also requires submission of three tables of adverse event information: One summarizing all serious adverse events; another one summarizing other adverse events that occurred with a frequency of 5 percent or more in any arm of the clinical trial; and finally, one summarizing all-cause mortality data by arm or group. This final rule clarifies that these adverse event tables must include information about events that occurred, regardless of whether or not they were anticipated or unanticipated. In addition, this rule requires responsible parties to provide the time frame for adverse event data collection and specify whether the collection approach for adverse events was systematic or non-systematic. The final rule does not require a responsible party to collect adverse event information that is not specified in the protocol (see Section IV.C.4).

Updates and Other Required Information

This final rule requires that all submitted information be updated at least annually if there are changes to report. More rapid updating is required for several data elements to help ensure that users of *ClinicalTrials.gov* have access to accurate, up-to-date information about important aspects of an applicable clinical trial or other clinical trial. The final rule also requires timely corrections to any errors discovered by the responsible party or the Agency during quality control review of submissions or after the information has been posted. The rule clarifies that the responsible party's obligation to submit updates and correction of errors ends on the date on which the required data elements for clinical trial results information have been submitted for all primary and secondary outcomes and all adverse events that were collected in accordance with the protocol, and the quality control review process has concluded (see Section IV.D.3).

Effective Date and Compliance Date

This final rule will be effective January 18, 2017. As of that date, the *ClinicalTrials.gov* system will allow responsible parties to comply with the rule. Responsible parties will have 90 calendar days after the effective date to come into compliance with the requirements of this rule (see Section IV.F).

Legal Consequences of Non-Compliance

This final rule outlines the potential civil or criminal actions, civil monetary penalty actions, and grant funding

actions that may be taken if responsible parties fail to comply with the rule's requirements. It does not outline all potential legal consequences, *e.g.,* laws governing the veracity of information submitted to the federal government, however, and should not be understood as describing the exclusive means of enforcement that the government might undertake with respect to compliance with the provisions of section 402(j) of the PHS Act, including these regulations (see Section IV. E).

Costs and Benefits

Based on our cost estimates, this regulatory action is expected to result in $59.6 million in annual costs, and it is not expected to have a significant impact on the economy. The costs consist primarily of the time needed to organize, format, and submit to *ClinicalTrials.gov* information that was prepared for or collected during the clinical trial (*e.g.,* summary of key protocol details and clinical trial results information). The potential benefits include greater public access to information about ongoing and completed applicable clinical trials. Such information may help potential clinical trial participants to better understand their options for participating in new trials; to better enable funders and clinical researchers to determine the need for new trials; to provide more complete information for those who use evidence from clinical trials to inform medical and other decisions; and to better enable the scientific community to examine the overall state of clinical research as a basis for engaging in quality improvement (*e.g.,* with regard to research methods). The rule is also expected to provide greater clarity about what is required for those who are subject to the legal mandate to submit information to *ClinicalTrials.gov* (see Section V).

Commonly Used Abbreviations

ANDA Abbreviated New Drug Application
API Application Program Interface
BLA Biologics License Application
CBER Center for Biologics Evaluation and Research, FDA
CDER Center for Drug Evaluation and Research, FDA
CDISC Clinical Data Interchange Standards Consortium
CDRH Center for Devices and Radiological Health, FDA
CFR Code of Federal Regulations
CONSORT Consolidated Standards of Reporting Trials
CSR Clinical Study Report
CTRP Clinical Trial Reporting Program, NCI
EMA European Medicines Agency
EU European Union
EudraCT European Clinical Trials Database
FDA Food and Drug Administration, HHS
FDAAA Food and Drug Administration Amendments Act of 2007
FDAMA Food and Drug Administration Modernization Act of 1997
FD&C Act Federal Food, Drug, and Cosmetic Act
FOIA Freedom of Information Act
FR Federal Register
HDE Humanitarian Device Exemption
HHS Department of Health and Human Services
ICH International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human Use
ICMJE International Committee of Medical Journal Editors
IDE Investigational Device Exemption
IND Investigational New Drug Application
IOM Institute of Medicine (now the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine)
IPD Individual Participant Data
IRB Institutional Review Board
IVD In Vitro Diagnostic
LPLV Last Patient Last Visit
MedDRA Medical Dictionary for Regulatory Affairs
MeSH® Medical Subject Headings
NCI National Cancer Institute, NIH
NCT National Clinical Trial
NDA New Drug Application
NIH National Institutes of Health, HHS
NLM National Library of Medicine, NIH
NPRM Notice of Proposed Rulemaking
OHRP Office for Human Research Protections, HHS
PCORI Patient-Centered Outcomes Research Institute
PDF Portable Document Format
PHS Act Public Health Service Act
PMA Premarket Approval
PRS Protocol Registration and Results System, *ClinicalTrials.gov*
RFA Regulatory Flexibility Act
SAP Statistical Analysis Plan
SNOMED CT® Systematized Nomenclature of Medicine—Clinical Terms®
UMLS Unified Medical Language System
U.S. United States
U.S.C. United States Code
U.S. TSA U.S. Trade Secrets Act
UTSA Uniform Trade Secrets Act, Uniform Law Commission
WHO World Health Organization
XML Extensible Markup Language

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I. Background

This final rule implements requirements for submitting registration and summary results information for specified clinical trials of drug products (including biological products) and device products to *ClinicalTrials.gov*, the clinical trial registry and results data bank operated by the NLM, NIH, since 2000. This final rule provides for the expanded registry and results data bank specified in 402(j) of the PHS Act (42 U.S.C. 282(j)), as amended by Title VIII of FDAAA and including technical corrections made to FDAAA under Public Law 110–316. These provisions are intended to enhance patient enrollment, provide a mechanism to track subsequent progress of clinical trials, provide more complete results information, and enhance patient access to and understanding of the results of clinical trials (see 42 U.S.C. 282(j), section 402(j) of the PHS Act).

The requirements apply to the responsible party (the sponsor or designated principal investigator) for certain clinical trials of drug products (including biological products) and device products regulated by the FDA under designated sections of the FD&C Act.

The Notice of Proposed Rulemaking (NPRM) for Clinical Trials Registration and Results Submission was published on November 21, 2014, in the FR (79 FR 69566). We received nearly 900 comments during the 120 day public comment period, which closed on March 23, 2015. Of the total comments received, about 60 percent were nearly identical in content, expressing support for clinical trial transparency efforts and the goals of the NPRM and provided specific perspectives on a number of the proposals. Another large subset of comments also expressed support for clinical trial transparency and the NPRM goals, but did not comment on specific proposals. There were about 100 distinct comments that addressed specific NPRM proposals. As reflected below, all of the comments were reviewed and all points and perspectives were carefully considered. Section III includes discussion of comments on several key issues in the final rule, and Section IV includes discussion of comments related to each specific provision in the final rule. For each key issue and specific provision, we outline the statutory basis, the NPRM proposal, the relevant public comments, our response to the comments, and the approach taken in the final rule. The NPRM provided a comprehensive review of the legislative background and history that led to its development and, by extension, to this final rule. We review it again here in brief.

NLM initially developed the database, known as *ClinicalTrials.gov*, in response to the statutory mandate of section 113 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) to establish, maintain, and operate a data bank of information on certain clinical trials (these requirements currently are codified at 42 U.S.C. 282(i), PHS Act 402(i)), and in support of NLM's statutory mission to improve access to information to facilitate biomedical research and the public health (see 42 U.S.C. 286(a)). The registry became publicly available in February 2000. Since the establishment of *ClinicalTrials.gov*, the scientific community, general public, and others have called for many new measures to improve access to and transparency of information about clinical trials. In addition, various parties have developed and implemented trial registration policies including, for example, journal editors (through the International Committee of Medical Journal Editors (ICMJE)) [Ref. 1, 2] and industry (through the International Federation of Pharmaceutical Manufacturers and Associations) [Ref. 3]. *ClinicalTrials.gov* accepts information on trials other than those legally required to be registered in support of the mission of the NLM and other policies such as those from the ICMJE [Ref. 1, 2]. With the enactment of Title VIII of FDAAA, the legal mandate for *ClinicalTrials.gov* reporting was expanded to include more registration information for a broader set of clinical trials, as well as results information.

As discussed in the proposed rule, there are significant public health benefits to requiring the disclosure of the information required under this rule. Enhancements to the scope of *ClinicalTrials.gov* improve its utility in assisting individuals in finding trials for which they may be eligible to enroll, and then ensuring that their participation is honored and trust is enhanced by creating a public record of the trial and its results. In addition, access to more complete information about clinical trials has both scientific and other public health benefits. The scientific benefits relate to the prevention of incomplete and biased reporting of individual trials, and the provision of information about a more complete and unbiased set of trials; the resulting set of data about clinical trials can form a more robust basis for current medical decision making and future research planning. In addition, *ClinicalTrials.gov* provides an overview of the clinical trials enterprise, facilitating quality improvement in study focus, design, and reporting. The rule should also provide greater clarity about what is required for those who are subject to the legal mandate to submit information to *ClinicalTrials.gov*.

For many years, members of the scientific community, general public, industry, and others have been in active discussions about the need for increased access to information about clinical trials [Ref. 4]. Communities have expressed concern about the lack of publications from clinical trials [Ref. 5] (regardless of outcomes) and bias in the literature, [Ref. 6, 7] which may be due to selective reporting by trial sponsors or by journals in response to manuscripts that they deem less interesting. Interested parties have highlighted the importance of filling this gap because of missed opportunities to share knowledge that could have had implications for research participants who took part in these trials, future research participants who may benefit from this missing knowledge in the design of studies in which they will participate, and patients who may have benefited from the missing information in terms of a more robust understanding of their diseases, conditions, and potential treatments.

Even before this rulemaking, extensive research had been conducted using the clinical trial information that is publicly available on *ClinicalTrials.gov*. The published literature relying on *ClinicalTrials.gov* data includes:

- Studies characterizing the clinical research for specific conditions, such as acute kidney injury and the assessment of endpoints and sample size in prevention trials [Ref. 8];
- studies identifying research gaps in a domain, such as for pediatric studies [Ref. 9];
- studies assessing data mining methods, such as the systematic identification of pharmacogenomics information from clinical trials [Ref. 10];
- studies characterizing the overall clinical research landscape, such as the characteristics of clinical trials registered in *ClinicalTrials.gov* [Ref. 11];

- studies evaluating publication bias or selective reporting, such as the lack of publication for trials registered on *ClinicalTrials.gov* [Ref. 12];
- studies of research reporting, for example, by examining discrepancies between the *ClinicalTrials.gov* results database and peer-reviewed publications [Ref. 13]; and
- studies assessing specific research-related methods and issues, such as the reporting of non-inferiority trials in *ClinicalTrials.gov* [Ref. 14] and the use of *ClinicalTrials.gov* to estimate condition-specific nocebo effects and other factors affecting outcomes of analgesic trials [Ref. 15].

Many commenters identified the issues noted above, and supported the need for greater access to information about clinical trials. A large majority of comments in response to the NPRM expressed support for the rule, with many noting the value of transparency of clinical trials, in general. Commenters highlighted that accessible information about trials is critical for the public, including patients, and will contribute to better science in various ways. For example, one commented that the proposed rule promotes transparency, benefitting patients in the long run. Another asserted that doctors work with uncertainty and that access to all results information, regardless of statistical significance, can be important. Others argued that requiring more trials to be registered and reported will allow science to progress more quickly because scientists will be able to learn from trials that they otherwise would not have had access to, helping them to avoid ''reinventing the wheel.''

On the other hand, we recognize that the posting of results information from applicable clinical trials of unapproved, unlicensed, and uncleared products, as well as unapproved, unlicensed, or uncleared uses of approved/licensed/cleared medical products, presents special challenges. Despite the concerns raised by opponents to the rule (such as concerns from device manufacturers and the pharmaceutical industry about disclosure of what they view to be proprietary, confidential information and its impact on innovation and investment incentives, and concerns that the delay for submission of results information is insufficient given the length and cost of drug development), it is important that results information for each such clinical trial of an unapproved, unlicensed, and uncleared product be presented in an unbiased manner, but with the understanding that the evaluation of the overall benefit and risk profile of each such product, or each use of an already approved product, be determined by an assessment of the full evidence base for that product (*i.e.,* not from the results of any one trial in isolation). Under the FD&C Act, the PHS Act, and their implementing regulations, firms that market medical products are generally required to submit an application to FDA for premarket review, and provide robust scientific evidence that demonstrates that the product is safe and effective for each of its intended uses, before the firm distributes the product for each such use. During FDA premarket review of medical products, FDA also generally reviews proposed labeling for the intended use(s) of the product to ensure that the labeling provides adequate information for the safe and effective use of the product. Real harms have been associated with use of medical products for unapproved uses—harms to health as well as the diversion of resources to ineffective treatments [Ref. 16, 17].

A. Review of Scientific Benefits Related to Specific Provisions of the Rule

Registration Information

A public registry of trials enables interested parties, including patients, to find trials in which they might want to participate and facilitates the discovery of trials for academic research centers with experts studying particular diseases or conditions [Ref. 18]. The highly structured data, along with the search engine, enable members of the public to search for trials that might meet their needs by using a variety of technical and non-technical terms [Ref. 19]. This is of particular importance for trials that involve unapproved, uncleared, or unlicensed medical products that might not have a generic name [Ref. 20]. These trials tend to use company-specific code names that *ClinicalTrials.gov* links to their eventual generic name (if one is assigned). As a result, a user of the system can find all trials associated with a given product, even if they use different names (or codes) at different stages of the product development cycle. Without such a registry, there would be no single, centralized way to identify trials studying any intervention for any disease regardless of sponsor or funding for which an individual may be eligible (*e.g.,* previous Federal trial registries established under the Health Omnibus Extension of 1988 for trials for human immunodeficiency virus infection and acquired immune deficiency syndrome, commonly referred to as HIV/AIDS, and FDAMA 113 for effectiveness studies for serious or life-threatening diseases or conditions conducted under investigational new drug applications (INDs) were limited to certain conditions and one intervention type, *i.e.,* drugs).

The public record also ensures that each individual's participation in a trial is appropriately respected by preventing the conduct of ''secret'' trials, for which their existence is not publicly known (and/or their results are never publicly reported after completion or misreported—*i.e.,* reporting bias) [Ref. 21, 22]. The unique identifier assigned to each record (NCT number) also permits, for the first time, a way to identify each clinical trial unambiguously [Ref. 23] and link information about a single clinical trial from different resources/databases [Ref. 24].

The searchable, structured listing of trials also enables Institutional Review Boards (IRBs) [Ref. 25], researchers, funding agencies, systematic reviewers [Ref. 26, 27], and other groups, including the Presidential Commission for the Study of Bioethics Issues [Ref. 28], and the National Academies of Science workshops [Ref. 29], to see the landscape of trials on a given topic, by a particular funder, by geography [Ref. 30], by population [Ref. 9], or other relevant criteria. Providing these users with such a capability informs their judgments about the potential value of new trials, scientific and financial accountability of sponsors, as well as helping to ensure that assessments of the risks and benefits of a potential intervention for a particular use account for the totality of evidence from all prior trials. Such analyses of the clinical research also provide feedback and insights for the clinical research community itself, by informing the design and analysis of future trials [Ref. 11, 31, 32].

The information that describes the clinical trial in the registry records also facilitates assessments of the quality and appropriateness of trial reporting by enabling journal editors, researchers, and other readers of the medical literature to assess the degree to which the disclosed results (*e.g.,* journal articles, scientific conferences) accurately reflect the prespecified protocol and have accounted for all prespecified outcome measures. This helps to (1) prevent the type of incomplete results reporting that has been documented in conference and journal abstracts, as well as in full journal articles [Ref. 33] and (2) allow the members of the public to assess fidelity to the protocol, which is essential to understanding the validity of disclosed results [Ref. 34].

The freely downloadable registry data enable third parties to use the information that describes the clinical trial to meet other specific needs [Ref. 35], such as reformatting the data for constituents of various patient advocacy groups (*e.g.,* patients with breast cancer) [Ref. 36], data mining for associations among interventions and diseases studied worldwide, and for use in semi-automated data collection for conducting critical appraisals and systematic reviews to support evidence-based medicine. For example, while *ClinicalTrials.gov* does not itself match potential participants with relevant trials, the rule ensures the timely posting of registration information about trials currently enrolling participants. This information is used by third parties to provide matching services that help patients find trials that might be appropriate for them.

Summary Results Information

The public availability of results information helps investigators design trials and IRBs review proposed trials, by allowing them to weigh the proposed study's risks and benefits against a more complete evidence base than is currently available through the scientific literature [Ref. 37]. The rule facilitates better science through aiding in the identification of knowledge gaps for trials of all types of products, whether unapproved or approved and marketed. Mandatory submission and posting of results information will also help investigators avoid repeating trials on drug and device products (including biological products) that have been found to be unsafe or unsuccessful while also providing access to information that may help verify findings.

While the registry information at ClinicalTrials.gov can be used to determine where information might be missing from the literature (*e.g.,* missing trials, missing outcome measures) [Ref. 13, 38, 39], the results database fills many gaps in the medical evidence base by providing tabular objective data that summarize findings from trials. These data can be used by systematic reviewers and others who analyze the literature to develop evidence-based treatment and policy recommendations [Ref. 26].

FDAAA has led to the development of a minimum reporting set that provides key facts about the aggregate analyses for each trial without the accompanying narrative interpretations found in journal articles[Ref. 40]. In this way, results are made available in a timely manner for all prespecified primary and secondary outcome measures, and all serious and frequent adverse events, and complement the published literature [Ref. 41].

The submission and posting of results information on *ClinicalTrials.gov* may occur before, simultaneously with, or after journal publication, but is independent of journal submission and publication. The legal requirements help to fill substantial gaps in the database left by the non-publication (or very delayed publication) of a substantial portion of clinical trials in the medical literature [Ref. 42, 43]. In addition, the complete set of results information for all primary and secondary outcome measures that were specified in a study protocol supplements the more limited set of results data found in the published literature [Ref. 44]. The availability of results information from applicable clinical trials will help to prevent skewing of the evidence base that is the foundation of systematic reviews and clinical practice guidelines. In addition, if information were to be presented publicly about the safety profile of an approved drug product, the availability of clinical trial results information through ClinicalTrials.gov could help inform the public record about the drug product's safety [Ref. 45].

Review of Public Health Benefits Related to Specific Provisions of the Rule

Results information for trials of unapproved products may inform the assessment of risks and benefits that potential participants might face in subsequent studies of those same or similar products; they may also contribute to the overall assessments that are made of similar marketed products [Ref. 46]. Trials of products that are unapproved, unlicensed, and uncleared are unlikely to be published if the results of these trials are insufficient to support applications for product approvals (*e.g.,* because the study resulted in negative findings or was inadequately designed or executed). This rule's requirements that responsible parties submit results information from clinical trials of unapproved, uncleared, or unlicensed products regardless of whether approval, clearance, or licensure is sought, as well as the public posting of this information, are expected to alleviate the concerns regarding bias in the literature and selective publication. Frequently cited economic benefits of sharing clinical trial data generally include avoiding a suboptimal return on the financial resources invested by study funders and sponsors [Ref. 47], while the submission and posting of results information from trials of unapproved, uncleared, or unlicensed products in particular is expected to reduce costs by minimizing the number of redundant trials. Overall, the rule's requirement ensures the public availability and accessibility of information that likely would not otherwise have been in the public domain.

The reporting of an unambiguous accounting for all deaths, as required by the final rule, within each trial enables researchers and others to understand the most basic elements of the study in a way that was not previously possible in many cases [Ref. 48].

Mandatory submission and posting of the protocol and statistical analysis plan (SAP) for each reported trial provides a resource for researchers and others interested in understanding the detailed methods used to conduct a particular trial and analyze the collected data [Ref. 49, 50, 51]. Our reasoning behind their inclusion is more fully explained in Section III.D on Submission of Protocols and Statistical Analysis Plans, but we wish to emphasize that availability of the protocol and SAP is expected to provide users of *ClinicalTrials.gov* with a fuller picture of the trial. One of the aims of the statute and of the rule is to ''provide more complete results information'' (section 402(j)(3)(D)(i) of the PHS Act), which we believe complements the goals of increased transparency and accountability. As such, the addition of the protocol as clinical trial results information to be submitted and posted on *ClinicalTrials.gov* furthers this statutory purpose and significantly enhances the understanding of the trial and the context of the data fields and results information provided. It also enables readers to conduct a more complete evaluation of results [Ref. 47, 52, 53]. Although protocols are sometimes provided along with published articles, they are currently distributed among different journal Web sites and cannot be reliably found for most trials. Protocols also help to provide a more nuanced understanding of key trial methods, including, for example, the detailed eligibility criteria; how information was collected for key outcome measures and adverse events; and how data were handled, including detailed methods of statistical analyses. Such details of trial methods can affect the interpretation of a study's findings [Ref. 52, 53, 54, 55]. SAPs describe the analyses to be conducted and the statistical methods to be used, including ''plans for analysis of baseline descriptive data and adherence to the intervention, prespecified primary and

secondary outcomes, definitions of adverse and serious adverse events, and comparison of these outcomes across interventions for prespecified subgroups. The full SAP describes how each data element was analyzed, what specific statistical method was used for each analysis, and how adjustments were made for testing multiple variables. If some analysis methods require critical assumptions, data users will need to understand how those assumptions were verified.'' [Ref. 47].

Limiting *ClinicalTrials.gov* to Objective Data

As described in greater detail in Section III.C on Submission of Technical and Non-technical Summaries, the final rule does not require the submission of technical or non-technical narrative summaries of study results due to a lack of evidence that such summaries would always meet the statutory standard of not being misleading or promotional (section 402(j)(3)(D)(iii)(I) and section 402(j)(3)(D)(iii)(II) of the PHS Act). In fact, experts suggest that such summaries can lead to biased reporting, whether because of omission or commission [Ref. 56]. Presenting results information in a tabular format leads to a more objective database. We believe that actively avoiding the introduction of bias serves an important public health interest—one that Congress foresaw—and prevents *ClinicalTrials.gov* from being a platform in which data are conflated with opinions or interpretation.

In this regard, it should be noted that nothing in this rule authorizes a firm to use information posted in, or links to, other Web sites available on *ClinicalTrials.gov* to promote unapproved, unlicensed, or uncleared medical products or unapproved, unlicensed, or uncleared uses of approved or cleared medical products, or supersedes or alters other statutory and regulatory provisions related to such communications. For example, under the FD&C Act, the PHS Act, and their implementing regulations, firms that market medical products are generally required to submit an application to FDA for premarket review, and provide robust scientific evidence that demonstrates that the product is safe and effective for each of its intended uses, before the firm distributes the product for each such use. To the extent firms make a product available for one use (whether as a medical product or not), but make express or implied claims regarding the safety or efficacy of that product for another medical product use, for which it lacks the applicable approval, licensure or clearance, they are effectively evading the premarket review requirements of the applicable law and undermining the public health interests advanced by these requirements.

In addition, where emerging and developing scientific data are not yet sufficiently complete or robust to demonstrate safety and efficacy of the product for an initial or additional intended use, representations of safety and effectiveness can be misleading, particularly if addressed to health care providers and/or patients [Ref. 57, 58]. Marketing activities and communications can also be designed to persuade, promote, and influence prescribing and use in ways that are not based on valid scientific evidence, to the extent such evidence exists [Ref. 59, 60].

It is important to note that even though we are limiting the submissions to objective data elements, the government does not independently verify the scientific validity or relevance of the information submitted to *ClinicalTrials.gov* beyond the limited quality control review by NIH, which is focused on the clarity and completeness of the information submitted, not the quality, validity, meaning or relevance of the trial itself. Accordingly, the inclusion of data and information in the *ClinicalTrials.gov* platform, the links to other studies and Web sites, and the conduct of the limited quality control review by NIH, do not constitute a government affirmation or verification that the information within or referenced in the database, or communications that rely on that information, are truthful and non-misleading.

Other Benefits

Other benefits relate to the role in assisting individuals in finding trials in which to enroll, and then ensuring that their participation is honored and trust is enhanced by creating a public record of the trial and its results. It also fulfills an obligation to trial participants that is established between them and the research team. Individuals participate in clinical trials with the understanding that the research will contribute to the expansion of knowledge pertaining to human health. When trial information is withheld from public scrutiny and evaluation, the interpretation of the data and the public's trust in the research may be compromised. The rule helps to further the goal of ensuring that participation in research leads to accountability via the public reporting of information. Much has been written about the importance of trust in clinical research, and although many factors promote the development of trust, ensuring a public record of the trials in which people participate contributes significantly to this goal [Ref. 47, 61].

Finally, the availability of results information is expected to assist people in making more informed decisions about participating in a clinical trial by providing them and their care providers with access to information about the results of a broader set of clinical trials of various interventions that have been studied for a disease or condition of interest.

B. Anticipated Long-Term Benefits of ClinicalTrials.gov Beyond the Final Rule

ClinicalTrials.gov provides the scaffolding on which individual participant data (IPD (the next frontier in transparency) and other trial ''meta-data'' can be organized in the future. This is particularly important to catalyze the enormous potential value of data sharing. Such IPD (and, for example, associated biospecimens) are most valuable if their availability is identified in a searchable system and associated with key trial meta-data so that they can be used in a scientifically appropriate manner. *ClinicalTrials.gov* provides mechanisms for linking the trial records with sources of IPD and meta-data about each trial as recommended by the Institute of Medicine (IOM)in a 2015 report entitled Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risks and ICMJE [Ref. 47, 62]; the search interface allows for the easy identification of such data so that researchers can identify data for their secondary use.

II. Overview of Statutory Provisions

The final rule clarifies and establishes additional procedures and requirements for registering and submitting results information, including adverse event information, for certain clinical trials of drug products (including biological products) and device products, as well as for pediatric postmarket surveillances of a device product that are required by FDA under section 522 of the FD&C Act; the final rule requirements implement section 402(j) of the PHS Act.

Title VIII of FDAAA, enacted on September 27, 2007, section 801(a), amended the PHS Act by directing the Secretary of the Department of Health and Human Services (HHS), acting through the Director of the NIH (or the Agency) to expand the existing clinical trial registry data bank known as *ClinicalTrials.gov* and to ensure that the data bank is publicly available through the Internet. Among other duties, NIH is

directed to expand the data bank to include registration information for a broader set of clinical trials than were required to register under FDAMA. Section 402(j) of the PHS Act specifies that identified entities or individuals, called responsible parties, are to submit registration information for certain applicable clinical trials of drugs (defined by section 402(j)(1)(A)(vii) of the PHS Act to include biological products) and devices, including any pediatric postmarket surveillance of a device required by FDA under section 522 of the FD&C Act (21 U.S.C. 360l). Section 402(j)(2)(A)(iii) of the PHS Act authorizes the Secretary of HHS to modify by regulation the data elements required for registration, provided that the Secretary provides a rationale for why such modification ''improves and does not reduce'' the information included in the data bank. The statute specifies certain deadlines by which registration information is to be submitted to the data bank.

Section 402(j)(3) of the PHS Act further directs the Agency to augment the registry data bank to include summary results information through a multistep process, as follows:

First, for those clinical trials that form the primary basis of an efficacy claim or are conducted after a product is approved, licensed, or cleared, the registry data bank is to be linked to selected existing results information available from the NIH and FDA (section 402(j)(3)(A) of the PHS Act). Such information includes citations to published journal articles focused on the results of applicable clinical trials, posted FDA summaries of FDA advisory committee meetings at which applicable clinical trials were considered, and posted FDA assessments of the results of any applicable drug clinical trials that were conducted under section 505A or 505B of the FD&C Act (21 U.S.C. 355a, 21 U.S.C. 355c).

Second, for each applicable clinical trial subject to section 402(j) of the PHS Act, the responsible party must submit to the data bank results information required under section 402(j)(3)(C) of the PHS Act. Such information is to include tables of demographic and baseline characteristics of the ''patients who participated in the clinical trial'' (section 402(j)(3)(C)(i) of the PHS Act), *i.e.,* the enrolled human subjects, and the primary and secondary outcome measures for each arm of the clinical trial, as well as a point of contact for scientific information about the clinical trial results and information on whether certain agreements exist between the sponsor and the principal investigator that limit the ability of the principal investigator to discuss or publish the results of an applicable clinical trial after it is completed. The *ClinicalTrials.gov* basic results component was launched on September 27, 2008.

In addition, section 402(j)(3)(I)(i) of the PHS Act directs the Secretary to issue regulations to ''determine the best method for including in the registry and results data bank appropriate results information on serious adverse and frequent adverse events for applicable clinical trials (required to submit results information under section 402(j)(3)(C) of the PHS Act) in a manner and form that is useful and not misleading to patients, physicians, and scientists.'' If regulations are not issued by September 27, 2009, then section 402(j)(3)(I)(ii) of the PHS Act specifies that the statutorily mandated adverse event reporting provisions specified in section 402(j)(3)(I)(iii) of the PHS Act shall take effect, requiring the submission of certain information summarizing serious and frequent adverse events observed during an applicable clinical trial. Regulations were not issued by the deadline, so the statutorily mandated adverse event reporting provisions required by sections 402(j)(3)(I)(ii) and (iii) of the PHS Act took effect on September 27, 2009, at which time the *ClinicalTrials.gov* basic results database was updated accordingly. Section 402(j)(3)(I)(v) of the PHS Act indicates that adverse event information is ''deemed to be'' clinical trial information that is included in the data bank pursuant to the requirements for results information submission under section 402(j)(3)(C) of the PHS Act.

Third, section 402(j)(3)(D) of the PHS Act requires the Secretary to further expand the data bank by regulation ''to provide more complete results information and to enhance patient access to and understanding of the results of clinical trials.'' It requires consideration of specific issues in developing the regulations, in particular:

(1) Whether to require submission of results information for applicable clinical trials of products that are not approved, licensed, or cleared (whether approval, licensure, or clearance was sought) (see section 402(j)(3)(D)(ii)(II) of the PHS Act.); and if submission of clinical trial results information is required for such applicable clinical trials, the date by which that information is required to be submitted. (See section 402(j)(3)(D)(iv)(III) of the PHS Act.);

(2) Whether non-technical written summaries of the clinical trial and its results can be included in the data bank without being misleading or promotional. (See section 402(j)(3)(D)(iii)(I) of the PHS Act.);

(3) Whether technical written summaries of the clinical trial and its results can be included in the data bank without being misleading or promotional. (See section 402(j)(3)(D)(iii)(II) of the PHS Act.);

(4) Whether to require submission of the full clinical trial protocol or only such information on the protocol as may be necessary to help evaluate the results of the trial. (See section 402(j)(3)(D)(iii)(III) of the PHS Act.);

(5) Whether the 1 year period for submission of results information should be increased to a period not to exceed 18 months. (See section 402(j)(3)(D)(iv)(I) of the PHS Act.); and

(6) Whether requirements for results information submission as set forth in the regulations should apply to applicable clinical trials for which results information required under section 402(j)(3)(C) of the PHS Act is submitted before the effective date of such regulations. (See section 402(j)(3)(D)(iv)(II) of the PHS Act.).

Section 402(j)(3)(D)(v) of the PHS Act further requires that the regulations shall establish:

(1) A standard format for the submission of clinical trial information. (See section 402(j)(3)(D)(v)(I) of the PHS Act.);

(2) Additional information on clinical trials and results written in nontechnical, understandable language for patients. (See section 402(j)(3)(D)(v)(II) of the PHS Act.);

(3) Procedures for quality control, with respect to completeness and content of clinical trial information, to help ensure that data elements are not false or misleading and are non-promotional. (See section 402(j)(3)(D)(v)(III) of the PHS Act.);

(4) Appropriate timing and requirements for updates of clinical trial information and whether and how such updates should be tracked. (See section 402(j)(3)(D)(v)(IV) of the PHS Act.);

(5) A statement to accompany the entry for an applicable clinical trial when primary and secondary outcome measures for such applicable clinical trial are submitted as a voluntary submissions after the date specified in section 402(j)(2)(C) of the PHS Act. (See section 402(j)(3)(D)(v)(V) of the PHS Act.); and

(6) Additions or modifications to the manner of reporting the data elements established under the results information submission provisions of section 402(j)(3)(C) of the PHS Act. (See section 402(j)(3)(D)(v)(VI) of the PHS Act.).

Section 402(j)(3)(D)(vii) of the PHS Act requires the Secretary to convene a public meeting to solicit input from interested parties on those issues. The public meeting was convened on April 20, 2009, on the NIH campus. The public meeting attracted more than 200 registered participants and 60 written comments. All of the comments received prior to, during, and after the public meeting are available in the Clinical Trials Public Meeting Docket, ID: NIH–2009–0002, at the *www.regulations.gov* Web site [Ref. 63]. We carefully reviewed the comments received in developing the proposed provisions to address the considerations enumerated in section 402(j)(3)(D) of the PHS Act. Many of the comments helped inform development of the proposed rule, which was issued on November 21, 2014, for public comment. For purposes of this rulemaking, we prepared a memorandum summarizing these comments from the public meeting and the issues commented upon [Ref. 64].

Furthermore, section 402(j)(4)(A) of the PHS Act directs that the data bank accept ''voluntary submissions'' of complete registration or complete results information for certain clinical trials for which such information would not otherwise be required to be submitted, provided that the responsible party complies with requirements that could involve submission of information on additional clinical trials.

Section 402(j)(5) of the PHS Act specifies certain procedures and penalties related to non-compliance. Among other things, it directs NIH to publicly post notices of noncompliance in the data bank; requires report forms under certain HHS grants to include a certification that required registration and results information submission under section 402(j) of the PHS Act are complete; requires federal agencies to verify compliance before future funding or continuation of funding under section 402(j) of the PHS Act; and grants FDA the authority to sanction responsible parties who fail to comply with section 402(j) of the PHS Act.

Section 801(b) of FDAAA includes certain conforming amendments to the FD&C Act, which make failure to comply with specified requirements of section 402(j) of the PHS Act, and the submission of false or misleading clinical trial information under section 402(j) of the PHS Act, prohibited acts under the FD&C Act (see 21 U.S.C. 331(jj)(1)–(3)). Committing any such prohibited act could subject the violator to criminal and/or civil penalties, including civil money penalties.

Section 801(c) of FDAAA requires the Secretary to issue guidance on how the requirements of section 402(j) of the PHS Act apply to a pediatric postmarket surveillance of a device, where that pediatric postmarket surveillance is not a clinical trial. The preamble of this final rule addresses this topic and is intended to serve as the required guidance.

Section 801(d) of FDAAA includes a preemption provision, which states that ''[u]pon the expansion of the registry and results data bank under section 402(j)(3)(D) of the PHS Act, as added by this section, no State or political subdivision of a State may establish or continue in effect any requirement for the registration of clinical trials or for the inclusion of information relating to the results of clinical trials in a database.''

III. Discussion of Public Comments on Selected Key Issues

A. Scope and Applicability

The final rule covers requirements for the submission of clinical trial registration and results information to the *ClinicalTrials.gov* database. It includes expanded requirements for the submission of clinical trial registration and results information, as authorized by section 402(j) of the PHS Act, to improve public access to information about certain clinical trials of FDA-regulated drug products (including biological products) and device products. However, the rule does not impose requirements on the design or conduct of clinical trials or on the data that must be collected during clinical trials. Instead it specifies how data that were collected and analyzed in accordance with a clinical trial's protocol are to be submitted to *ClinicalTrials.gov*.

Following the public comment period, we received comments on a variety of the NPRM's sections and key issues, which are discussed in detail in the other subsections of Section III and in Section IV of this preamble. We also received comments from approximately 115 commenters on topics that, while important, are outside of the scope of the NPRM and the rule. Although we are not responding to these comments, the types of topics raised by these comments are described below.

We received comments suggesting that the rule should establish requirements for the conduct of clinical trials and that compliance with the rule should affect whether future clinical trials may proceed. For example, it was suggested that the rule should not permit trials with placebo groups to be conducted where there is no benefit to the participant and the condition studied is life-threatening. It was also suggested that studies should not be allowed to proceed to the next phase until all information submission requirements of the rule are met. We emphasize neither section 402(j) of the PHS Act nor this rule establishes requirements for clinical trial design or progress.

Commenters also provided input on the role of human subjects review boards, suggesting that the rule should require all proposed studies to be subject to their review, and that the rule should clarify HHS' position on human subjects protection. The role of human subjects review boards in the course of research is outside of the scope of this rule, but Human Subjects Protection Review Board Status is a required registration data element (see §§ 11.10(b)(35) and 11.28(a)(2)(iv)(D)).

Commenters also provided input on how they see the role of the rule with respect to FDA action. For example, it was suggested that the rule should prohibit the approval of a product application submitted to FDA unless results information submission requirements have been met. While the rule's results information submission requirements are connected to FDA approval, licensure, or clearance in terms of triggers for results information submission in certain cases, the rule does not affect, direct, or prohibit FDA from acting on a particular application or submission. Although FDA's actions with respect to approval, licensure, or clearance are outside the scope of this rule, FDA enforces FDAAA's registration and results information submission requirements and the requirement that a responsible party not submit false and/or misleading information. As described in more detail in Section IV.E, if FDA identifies a violation, the Agency may notify the responsible party and, as appropriate, initiate administrative proceedings for civil monetary penalties or the process for civil or criminal judicial actions.

We received comments about enforcement of the rule, suggesting that NIH and FDA should be enforcing the current requirements (*i.e.,* before the rule's effective date) as well as the additional results information reporting requirements in the final rule. We have addressed the applicability of the requirements of section 402(j) of the PHS Act and final rule throughout this preamble, including in the Effective Date, Compliance Date, and Applicability of Requirements in this Part discussion in Section IV.F. A few commenters suggested that FDA should enforce results information reporting requirements and that it should cancel

marketing approvals ''in cases of egregious misrepresentations.'' Commenters also proposed specific penalty structures, such as only penalizing the responsible party and not the institution and making all intentional violations criminal with mandatory prison sentences. They also proposed incentives, such as providing easier submission mechanisms and citable credit for shared data sets. The specifics of how and under what circumstances FDA will seek to enforce section 402(j) of the PHS Act are beyond the scope of the rule, as are issues relating to the marketing of FDA-regulated products. FDA may issue guidance regarding enforcement in the future. FDA enforces FDAAA's registration and results information submission requirements and the requirement that a responsible party not submit false and/or misleading information. As described in more detail in Section IV.E, if FDA identifies a violation, the Agency may may notify the responsible party and, as appropriate, initiate administrative proceedings for civil monetary penalties or the process for civil or criminal actions.

Although we did include in the preamble to the proposed rule a general discussion of the statutory procedures and penalties related to non-compliance (79 FR 69570), we did not otherwise discuss in detail the legal ramifications of failure to comply with the requirements of section 402(j) of the PHS Act, including these regulations. Other than the requirement that a responsible party not submit false or misleading information and the associated notice of potential liabilities for doing so (see § 11.6), the proposed codified text did not describe the potential legal consequences of failing to comply with the requirements of the rule. However, as discussed in Section IV. E below, we are adding a new § 11.66 that describes potential legal consequences provided for in the FDAAA enforcement provisions for failure to comply with the requirements in these regulations.

Some commenters suggested that the rule should require registered trials to make IPD datasets available to qualified researchers and some suggested that the rule should require the submission and disclosure of de-identified IPD datasets to *ClinicalTrials.gov*. The sharing or submission of de-identified IPD is not required or authorized in section 402(j) of the PHS Act, and is, thus, not included in this rule. In addition, *ClinicalTrials.gov* does not currently have a mechanism to directly collect datasets containing de-identified IPD. As discussed in Section I, however, *ClinicalTrials.gov* provides optional registration data elements that allow responsible parties to specify whether there is a plan to share the IPD or associated documents from the trial. Providing such meta-data about IPD in a searchable system facilitates identification of such data for use in a scientifically appropriate manner. In this way, we anticipate that *ClinicalTrials.gov* can be used in the future to catalyze IPD sharing.

Some commenters expressed concern about whether posting results information might be considered ''prior publication'' by journal editors thereby precluding subsequent publication of a journal article, while others suggested that posting of results information could be delayed an additional 12 months while papers undergo peer review. The rule implements the directives of section 402(j) of the PHS Act and is independent of the ICMJE clinical trial registration policy [Ref. 1, 2]. However, we note that the ICMJE has stated that submission of summary results to *ClinicalTrials.gov* will not be considered prior publication and will, thus, not interfere with journal publication [Ref. 2]. Interested parties are encouraged to explore the policies of the ICMJE and of the journals to which they seek to submit papers.

Some commenters also requested that NIH publish guidance clarifying the rule's requirements and provide training to clinical investigators about them. The Agency intends to continue making guidance documents and other materials available, including examples, case studies, and, as discussed below, a publicly-accessible checklist-based tool available at *https://prsinfo.clinicaltrials.gov* (or successor site) consisting of the relevant data elements and detailed explanation of each criterion. One commenter also suggested that one of the reasons for poor compliance with current law is the difficulty in interpretation and complexities around results reporting. We expect that the clarifications in this rule will help to address this concern.

Commenters provided suggestions regarding the usability of *ClinicalTrials.gov*. Comments regarding technical changes to the Web site are discussed in Section IV.A.4 (''In what format must clinical trial information be submitted?—§ 11.8''). While the details of the usability of *ClinicalTrials.gov* were not outlined in the NPRM or codified in this rule, we do wish to address these comments. Some commenters were dissatisfied with the process for entering data into the Protocol Registration and Results System (PRS), noting it is difficult to navigate, cumbersome, and complex. The PRS is the electronic system maintained by *ClinicalTrials.gov* that responsible parties use to register and submit results information for their studies, described at *https://prsinfo.clinicaltrials.gov*. They pointed to limitations of the PRS in sorting, filtering, and building queries, and some had specific suggestions on elements by which the site should be able to search, filter, and sort. We note that the PRS user interface has been updated incrementally over time with significant changes being made between 2014 and 2016, including the implementation of features to help streamline the results data entry process. In addition, based on usability study findings and expert evaluation, we further streamlined the data submission process for registration and results information, improved the reporting and portfolio management functions (with this series of enhancements, including one made in March 2016, addressing many of the concerns expressed by commenters), and provided enhanced resource materials for data submitters. We have also been providing 1-on-1 assistance to investigators submitting results in the PRS. While we continue our efforts to enhance the usability of the PRS and train personnel at academic institutions to provide centralized support to their investigators, the 1-on-1 assistance initiative has proven to be effective for providing customized support to investigators in fulfilling their requirements—especially for the many investigators who are using the PRS to submit results information for the first time. We will also expand the options in the PRS to accommodate the requirements of the final rule.

Commenters wanted the site to be user-friendly and allow for feedback, suggesting the NIH consult with experts to develop tools and with members of the public to ensure a user-friendly interface. We have conducted usability studies with a wide user audience and continue to obtain valuable feedback from a survey implemented on the public site. An example of a change that was made using this feedback was adding an option to search for trials based on the specific age of the potential participant (previously only age groups were easily searchable). We note that users may continue to provide feedback by using the ''Contact NLM Help Desk'' link on the bottom of every page on the *ClinicalTrials.gov* public Web site and by responding to the survey, when prompted. We intend to further consider this valuable input and collect

additional input as we continue to refine the site and optimize it to support provider and patient needs and to improve its scientific utility. Our goal is for clinical researchers, data scientists, health care providers, patients, and the public users of the site to have a more positive experience and for the site to be functional for these diverse audiences.

Other commenters wanted to be sure the Agency has sufficient resources to carry out NLM's mission. Commenters also requested better communication between the *ClinicalTrials.gov* staff that operate the PRS and responsible parties, particularly via email, and suggested that the NIH reinstate in-person training sessions. Over the last year, we have expanded both the customer service and reviewer staff and provided comprehensive training to help ensure communications with responsible parties are as prompt, clear, and helpful as possible. We will continue to ensure staff are well-trained and monitor the satisfaction of responsible parties with the communications they receive. We will continue to offer PRS training to responsible parties. In addition, we will be launching a series of activities, such as webinars and presentations at selected conferences, to educate the biomedical research community about their obligations and to ensure that patients and care providers are aware of the information available at *ClinicalTrials.gov*. All such information will be available from *https://prsinfo.clinicaltrials.gov*. Overall, we are taking steps to improve the usability of the resource for all users of *ClinicalTrials.gov*, data submitters and data users alike.

Finally, a few commenters suggested that the law and the final rule should apply to all researchers conducting clinical trials with NIH funds. A number of commenters also took note of the proposed NIH Policy on Dissemination of NIH-Funded Clinical Trial Information, which was issued by NIH on November 19, 2014, in tandem with the publication of the NPRM [Ref. 65]. The policy proposed that all NIH-funded awardees and investigators conducting clinical trials should be expected to register their clinical trials and submit results information to *ClinicalTrials.gov*. NIH proposed that the policy would apply to awardees and investigators conducting clinical trials, funded in whole or in part by NIH, whether or not they are subject to section 402(j) of the PHS Act. The policy would, thereby, also apply to NIH-funded phase 1 clinical trials of FDA regulated drugs, small feasibility studies of devices, and trials of interventions not regulated by FDA, including surgical and behavioral interventions.

The draft policy proposed that the same registration and results information submission elements and reporting timeframes that would be required under the final rule would also apply to those clinical trials subject to the NIH policy, through the terms and conditions of the NIH funding awards. Most of the NPRM commenters who also commented on the draft NIH policy were supportive of it and of its application to a wider range of clinical trials [Ref. 66]. NIH considered those comments and comments received on the policy itself in developing the final policy. The final policy is substantively the same as the proposed draft policy in terms of scope, applicability, and the content and timing of registration and results information submission. It requires NIH-funded applicants and offerors to submit a plan for the dissemination of NIH-funded clinical trial information that will address how the policy's expectations for registration and results information submission will be met. NIH-funded awardees and investigators conducting clinical trials funded in whole or in part by NIH will be required to comply with all terms and conditions of award, including following their plan for the dissemination of NIH-funded clinical trial information. The final NIH policy, NIH Policy on Dissemination of NIH-Funded Clinical Trial Information, appears elsewhere in this FR [FR OFFICE, PLEASE CROSS–REFERENCE NIH POLICY] and includes a preamble discussing the public comments on the draft policy.

B. Submission of Results Information for Applicable Clinical Trials of Unapproved, Unlicensed, or Uncleared Products for Any Use

Overview of Proposal

Section 402(j) of the PHS Act requires the submission and posting of registration information and results information for applicable clinical trials of approved, licensed, or cleared products, as well as submission of registration information and posting requirements for applicable clinical trials of unapproved, unlicensed, or uncleared products. The statute provides the Secretary with the discretion through rulemaking to require the submission of results information from applicable clinical trials of products that are unapproved, unlicensed, or uncleared, whether or not approval, licensure, or clearance was sought. In particular, section 402(j)(3)(D)(ii)(II) of the PHS Act specifies that the Secretary, through regulation, shall establish whether results information should be required for ''(aa) an applicable drug clinical trial for a drug that is not approved under section [505 of the FD&C Act] and not licensed under section [351 of the PHS Act] (whether approval or licensure was sought or not); and (bb) an applicable device clinical trial for a device that is not cleared under [section 510(k) of the FD&C Act] and not approved under section [515 or section 520(m) of the FD&C Act] (whether clearance or approval was sought or not).'' Given this authority and various factors discussed in the NPRM (79 FR 69633), we proposed to require submission of results information from applicable clinical trials of FDA-regulated drugs (including biological products) and devices that are unapproved, unlicensed, or uncleared for any use as of the completion date, whether or not approval, licensure, or clearance was sought.

Regarding the scope of trials for which submission of results information in accordance with subpart C of the proposed rule is required, § 11.42(a) proposed to require submission of results information for all applicable clinical trials (*i.e.,* regardless of whether the product being studied was approved, licensed, or cleared) for which submission of registration information was required under proposed § 11.22 and for which the completion date was on or after the effective date of the rule. Section 11.42(b) proposed to require submission of results information for those applicable clinical trials for which submission of registration information was required under proposed § 11.22 and for which the completion date was before the effective date of the rule, but for which the relevant results information submission deadline in proposed § 11.44 was on or after the effective date of the rule and results information was submitted on or after the effective date, consistent with the applicable deadline established by proposed § 11.44.

With respect to the proposed results information submission deadlines for applicable clinical trials of drugs and devices that are not approved, licensed, or cleared by FDA for any use as of the completion date of the trial (where the completion date occurs prior to the effective date of the final rule), but are subsequently approved on or after the effective date, proposed § 11.44(a)(2) would require results information to be submitted by the earlier of (i) 1 year after the primary completion date or (ii) 30 calendar days after FDA approval,

licensure, or clearance, except as otherwise provided under § 11.44(c), (d), or (e). Under proposed § 11.44(c), results information submission for applicable clinical trials studying FDA-regulated drugs (including biological products) or devices that were not approved, licensed, or cleared by the FDA for any use before the completion date of the trial may be delayed for up to 2 additional years (*i.e.,* up to 3 years after the primary completion date) if the responsible party certifies before the results information submission deadline that initial approval, licensure, or clearance of the studied product is being sought or may be sought by the sponsor at a future date. If the responsible party so certifies, all required clinical trial results information must be submitted by the earlier of (1) 30 calendar days after FDA approves, licenses, or clears the drug or device for any indication studied in the applicable clinical trial, (2) 30 calendar days after a marketing application or premarket notification is withdrawn and not resubmitted within 210 calendar days, or (3) 2 years from the date of certification (proposed § 11.44(c)(2)). Proposed § 11.44(d) addressed the submission requirements in situations where clinical trial results information has not been collected for a secondary outcome measure by the completion date.

The NPRM also addressed the situation in which results information for an applicable clinical trial of a device not previously approved or cleared is required to be submitted. Proposed § 11.35(b)(2) implemented section 402(j)(2)(D)(ii)(I) of the PHS Act, which prohibits the Director from posting submitted registration information prior to the date on which FDA approves or clears the device studied in the applicable clinical trial. Therefore, the timelines for submitting and posting clinical trial results information for applicable device clinical trials for unapproved or uncleared devices in proposed §§ 11.44 and 11.52, respectively, could result in the public availability of clinical trial results information for such trials before the information submitted during registration is posted in accordance with proposed § 11.35(b)(2) for these same trials, and for devices that are never approved or cleared, without such registration information ever being posted.

As we explained in the NPRM, posting clinical trial results information without sufficient corresponding public availability of certain descriptive information about the trial (that is similar to the type of information included as part of registration) would fail to provide the necessary context for understanding clinical trial results information, thereby significantly limiting understanding of posted results information (79 FR 69580). Section 402(j)(3)(D)(ii)(II) of the PHS Act authorizes the Secretary to require, through rulemaking, the submission of clinical trial results information for applicable clinical trials of products that have not been approved, licensed or cleared, whether or not approval, licensure or clearance had been sought. Specifically, it authorizes the Secretary to require, for an applicable device clinical trial of a device that has not been previously approved or cleared, the submission of the results information that is described in section 402(j)(3)(D)(iii) of the PHS Act. Section 402(j)(3)(D)(iii) of the PHS Act states that the regulations ''shall require, in addition to the elements described in [section 402(j)(3)(C) of the PHS Act] . . . [s]uch other categories as the Secretary determines appropriate.'' Thus, for applicable device clinical trials of unapproved or uncleared devices, the Secretary can require, through rulemaking, submission of ''such other categories'' of results information as the Secretary determines appropriate in addition to the information required under section 402(j)(3)(C) of the PHS Act. As discussed in the NPRM, in order to ''enhance patient access to and understanding of the results of clinical trials'' as required by section 402(j)(3)(D)(i) of the PHS Act, we interpreted ''such other categories'' of results information for applicable device clinical trials of unapproved or uncleared devices subject to proposed § 11.35(b)(2) and for which posting of registration information continues to be delayed to include, among other things, certain descriptive information that is similar to the type of information that is required to be submitted under section 402(j)(2)(A)(ii) of the PHS Act (79 FR 69581). Accordingly, proposed § 11.48(a)(6) required responsible parties for applicable device clinical trials of unapproved or uncleared devices, for which the device remained unapproved or uncleared at the time of results information submission to submit this descriptive information as part of clinical trial results information.

Comments and Response

A number of commenters addressed the topic of results information submission for applicable clinical trials of unapproved, unlicensed, or uncleared products. Commenters who supported the proposal stated that public availability of results information from trials of unapproved, unlicensed, and uncleared drugs (including biological products) and devices is expected to have public health benefits, as it helps protect the safety of participants who volunteer to be in clinical trials by reducing the likelihood that people will unknowingly design, approve, or participate in clinical trials that are duplicative and unnecessary (*e.g.,* because similar clinical trials have already been conducted but not published), or that are potentially ineffective or harmful (*e.g.,* because similar interventions have been shown to be harmful or ineffective in previous, unpublished clinical trials). Commenters also stated that results information from trials of unapproved, unlicensed, or uncleared products will reduce costs by minimizing the number of redundant trials.

Commenters expected that public availability of results information will assist potential human subjects in making more informed decisions about participating in a clinical trial by providing them and their care providers with information about the results of a broader set of clinical trials of various interventions that have been studied for a disease or condition of interest. Investigators and human subjects protection review boards that already have access to unpublished information from the sponsor of a clinical trial or the manufacturer of a drug or device will have access via *ClinicalTrials.gov* to information about other clinical trials of similar unapproved, unlicensed, or uncleared products that might help them in designing or considering the potential risks and benefits of participation in a clinical trial.

Commenters highlighted that results should be put to the broadest use because participants in research often put themselves at risk to participate and they deserve to have their participation contribute to the advancement of medical science, so that future patients may benefit from the knowledge gained. Commenters also indicated that increased transparency could help researchers learn from failed trials, verify findings, advance research, and improve overall understanding of disease. Commenters stated that trial results that are never published distort the evidence base for systematic reviews conducted to support development of clinical practice guidelines, which increases the time and effort needed to develop such guidelines. One commenter suggested that because it is common for products to be used outside of their approved marketing authorization in medical practice, information on trials of unapproved, unlicensed, or uncleared products

should comply with robust reporting requirements in order to minimize potential risk to the public.

A couple of commenters mentioned that the requirement to submit results information from trials of unapproved products is consistent with the 2014 European Union (EU) clinical trial regulations. We agree with this point and note the ongoing regulatory efforts by the European Medicines Agency (EMA) to make results information from clinical trials of drugs conducted within the EU available in a publicly accessible data bank, regardless of the approval status of the drug [Ref. 67, 68, 69]. As discussed in the NPRM, all clinical trials of drugs performed within the EU are registered in EMA's European Clinical Trials Database (EudraCT) database, with information on phase 2, 3, and 4 clinical trials and all pediatric clinical trials made public through the EU Clinical Trials Register (79 FR 69578) [Ref. 70]. In October 2013, EMA released a new version of the EudraCT database to support the submission and public posting of summary clinical trial results on the EU Clinical Trials Register (EU CTR). The specified summary results information differs from the detailed information that would be submitted to EMA as part of a Marketing Authorization Application. As noted in the EMA's announcement, the EudraCT summary results data requirements are ''substantially aligned'' with those of the ClinicalTrials.gov results database [Ref. 71].

Commenters who were opposed to the proposal suggested that submission (and public posting) of results information for trials of products still under development may curtail incentives to invest in innovative research. Regarding devices in particular, it was suggested that requiring results information submission for trials of uncleared devices will have a negative effect on the development of new and innovative devices. Comments suggested that the risk of disclosing such results information would outweigh the benefit to the public, who cannot use a product that is not approved, licensed, or cleared. See the discussion of § 11.44 in Section IV.C.3 of this preamble for comments and the Agency response regarding the timeline for submission of results information for trials of unapproved, unlicensed, or uncleared products.

Several commenters raised legal challenges, citing the FD&C Act, the Freedom of Information Act (FOIA), and the U.S. Trade Secrets Act (U.S. TSA). We disagree with these comments. As an initial matter, we would like to clarify that FDA's disclosure laws and regulations do not apply to information submitted to *ClinicalTrials.gov*. FDA's statutory provisions apply to information obtained by the FDA pursuant to the enumerated statutory provisions of the FD&C Act, (see sections 301(j) and 520(c) of the FD&C Act) and FDA's general and product-specific disclosure regulations for drug products (including biological products) and device products apply to FDA records. (See 21 CFR part 20 and 21 CFR 312.120, 314.430, 807.95, 812.38, and 814.9). Information submitted to *ClinicalTrials.gov* is submitted to NIH pursuant to section 402(j) of the PHS Act and the regulations promulgated under it. Registration and results information submitted to *ClinicalTrials.gov* is not obtained pursuant to the FD&C Act, nor is it maintained as an FDA record.

With respect to the FOIA (5 U.S.C. 552), although the FOIA provides a general right to obtain information in Federal Agency records, it also establishes certain exemptions from disclosure; thus, while the FOIA is, broadly speaking, a disclosure statute, it also states that the disclosure requirements do not apply to information in Agency records if that information falls within one of the enumerated exemptions (see 5 U.S.C. 552(b)). In other words, an Agency is not required to release information under FOIA if that information falls within one of the enumerated exemptions. One of the categories of information that is exempted from disclosure is ''trade secrets and commercial or financial information obtained from a person [that is] privileged and confidential.'' (5 U.S.C. 552(b)(4)). In contrast, the U.S. TSA (18 U.S.C. 1905) explicitly prohibits the release of such information by an Agency employee from Agency records. However, the U.S. TSA prohibitions do not apply when the disclosure of information is authorized by law. As established by the Supreme Court in *Chrysler Corp.* v. *Brown,* 441 U.S. 281 (1979), a statute or validly promulgated regulation requiring disclosure constitutes ''authorization by law'' for purposes of the U.S. TSA. Section 402(j) of the PHS Act requires that the Agency post certain registration and results information from applicable clinical trials, and further requires the Secretary to determine via rulemaking whether to require the submission and posting of results information from applicable clinical trials of unapproved, unlicensed, or uncleared drugs and devices (see section 402(j)(3)(D)(i) and (ii)(II) of the PHS Act), as well as to determine what results information must be submitted (see section 402(j)(3)(D)(iii)(IV) of the PHS Act). Accordingly, to the extent that clinical trial information, including but not limited to results information from applicable clinical trials of unapproved, unlicensed, or uncleared drugs and devices, described in section 402(j) of the PHS Act and this final rule may contain trade secret and/or confidential commercial information, the requirement that such information be posted on *ClinicalTrials.gov* is authorized by law for the purposes of the U.S. TSA.

It was also suggested that the provision in section 402(j)(2)(D)(ii)(I) of the PHS Act for delayed disclosure of registration information prohibits the posting of results information for applicable clinical trials of unapproved or uncleared devices. We believe the authority to require submission of results information for applicable clinical trials of unapproved and uncleared devices is clear from the language in section 402(j)(3)(D)(ii)(II)(bb) of the PHS Act. We have explained above the reasoning for requiring responsible parties to submit certain descriptive information as part of clinical trial results information for certain applicable device clinical trials of unapproved or uncleared device products, which is maintained in the final rule at § 11.48(a)(7).

One commenter also suggested that disclosure would be a forced release of trade secrets and confidential commercial information in violation of common law applicable to trade secrets. Another commenter raised a constitutional challenge, suggesting that the Agency would be disclosing trade secrets through this requirement, which they argued would constitute a regulatory taking of property without just compensation, in violation of the Fifth Amendment of the U.S. Constitution. We disagree.

The Supreme Court found in *Ruckelshaus* v. *Monsanto* (467 U.S. 986 (1984)) that trade secrets are property for purposes of the application of the Takings Clause of the Fifth Amendment. Most states have adopted the Uniform Trade Secrets Act (UTSA) and its definition of ''protected trade secret interests'': ''[I]nformation, including a formula, pattern, compilation, program, device, method, technique, or process that: (i) Derives independent economic value, actual or potential, from not being generally known to, and not being readily ascertainable by proper means by, other persons who can obtain economic value from its disclosure or

use, and (ii) is the subject of efforts that are reasonable under the circumstances to maintain its secrecy.'' (See UTSA with 1985 Amendments § 1(4)).

However, even if there is a protected trade secret interest, the question of whether the government's proposed regulation amounts to a taking under the Fifth Amendment requires additional analysis. In *Penn Cent. Transp. Co.* v. *City of New York* (438 U.S. 104 (1978)), the Supreme Court set forth a three-factor analysis for determining whether a regulatory taking had occurred. Specifically, the Court identified (1) The extent to which an Agency's regulation interferes with distinct investment-backed expectations, (2) The economic impact of the regulation on the claimant, and (3) The character of the governmental action.

As an initial matter, none of the commenters identified any specific information that they assert constitutes trade secret information for purposes of a takings analysis, and that would be taken as a result of the statutory and regulatory requirements regarding submission to and posting on *ClinicalTrials.gov*. With respect to the factors outlined by the Supreme Court in *Penn Central,* we do not believe that drug and medical device manufacturers have a reasonable expectation at this time that the results information described in the final rule will be kept confidential. This is because (1) the field of drug and device development is highly regulated, (2) there has been robust public debate over the need for greater transparency of clinical trial results, and (3) it has been clear since the proposed rule was issued in 2014 (and in our view since the enactment of FDAAA, with its requirement that the rulemaking address the issue of results information submission and posting for applicable clinical trials of unapproved, unlicensed, and uncleared products), that such information can and may be made available to the public. None of the commenters have identified specific information required under the regulations that they believe would be of value to competitors, or that would allow competitors to benefit from innovators' scientific and technical advancements. Nor, as stated above, have they identified specific clinical trial results information that would be required to be submitted and that would meet the definition of a protected trade secret property interest for purposes of a takings analysis.

Regarding the final factor under *Penn Central,* we reiterate that, as discussed at length in this preamble, as well as in the proposed rule, there are significant public health benefits to requiring the disclosure of the information posted on *ClinicalTrials.gov*, including for applicable clinical trials of unapproved, unlicensed, and uncleared products. For many years the scientific community, general public, industry and others have engaged in high-profile public discussions about the need for increased access to information about clinical trials. Potential societal harms associated with having an incomplete medical evidence base have been reviewed; for example, studies have revealed that selective publication of clinical trial results could give a misleading picture about serious adverse effects of widely marketed drugs and about increased risks of such effects in certain segments of the population [Ref. 45].

As noted previously, the requirements for submission to and posting on *ClinicalTrials.gov* have the additional public health benefit of supporting international standards and norms (*e.g.,* Declaration of Helsinki, World Health Organization (WHO) Statement on Public Disclosure of Clinical Trials Results) and with industry, governmental, and other policies. The requirements under section 402(j) of the PHS Act, including those in this final rule, reflect our careful consideration and balancing of the burdens and benefits of the disclosure of this information for the drug and medical device industry and the public. These requirements further the important public health goals of enhancing patient enrollment in clinical trials, providing a mechanism to track the progress of clinical trials, and enhancing patient access to and understanding of the results of clinical trials.

The final rule maintains the proposal to require the submission of results information for applicable clinical trials of unapproved, unlicensed, or uncleared products, regardless of whether FDA approval, licensure, or clearance is or will be sought or obtained. We conclude that this requirement is in furtherance of the express statutory purpose of section 402(j)(3)(D)(i) of the PHS Act, which states that the Secretary shall expand the registry and results data bank ''[t]o provide more complete results information and to enhance patient access to and understanding of the results of clinical trials.'' We considered a number of factors, notably the potential public health benefits of timely disclosure of results information for applicable clinical trials of unapproved, unlicensed, or uncleared products; the potential effects of disclosure on the competitive advantage of drug and device manufacturers, including incentives to invest in the development of new products intended to improve public health; and other results information submission requirements and policies (*e.g.,* those of the EMA). Other considerations include the relative burden on the responsible party of submitting results information for an applicable clinical trial of an unapproved, unlicensed, or uncleared product, the date by which results information must be submitted and practical issues of implementation and compliance.

As discussed in the NPRM (79 FR 69578), we recognize that the posting of results information about applicable clinical trials of unapproved, unlicensed, and uncleared products presents special challenges. Such information would be accessible to care providers and their patients but describe products that are not approved, licensed, or cleared, and thus may not be available outside of clinical trials. Further, even for approved, licensed, or cleared products, the posted results information might contain information about unapproved, unlicensed, or uncleared uses and further information may be helpful in understanding potential risks and benefits. We believe that the results information from any individual applicable clinical trial should be considered in the context of the broader set of information available about the product and alternative products. In keeping with current practice, we intend to establish links from clinical trial records in *ClinicalTrials.gov* to additional sources of information, including but not limited to the FDA and NIH information specified in section 402(j)(3)(A)(ii) of the PHS Act (we intend to indicate that the links were added by the Agency and not by the responsible party for the applicable clinical trial). We intend to provide information to assist users in better understanding and interpreting the information available in *ClinicalTrials.gov*, including materials that describe the general purpose and content of the data bank, a general description of the limitations of the results information presented, and cautions that the information should be used in conjunction with advice from healthcare professionals.

In this regard, it bears repeating that nothing in this rule authorizes a firm to use information posted in, or links to other Web sites available on, *ClinicalTrials.gov*, to promote unapproved, unlicensed, or uncleared medical products or unapproved, unlicensed, or uncleared uses of approved, licensed, or cleared medical products, or supersedes or alters other statutory and regulatory provisions

related to such communications. In addition, the government does not independently verify the scientific validity or relevance of the information submitted to *ClinicalTrials.gov* beyond the limited quality control review by NIH. As discussed in Section III.C.12 of the NPRM, since responsible parties have been submitting results, the NIH has used a two-step process for quality control, starting with an automated system-based check prior to submission followed by a detailed, manual review after submission. This detailed review is based on quality review criteria for identifying apparent errors, deficiencies, or inconsistencies that are not detected by the automated checks. If any such problems are identified in the detailed, manual review, the proposed rule stated, the Director would send an electronic notification to the responsible party, indicating that the submission contains apparent errors, deficiencies, and/or inconsistencies listing such issues and requesting that they be addressed. Accordingly, the inclusion of data and information in the *ClinicalTrials.gov* platform, the links to other studies and Web sites, and the conduct of the limited quality control review by NIH, do not constitute a government affirmation or verification that the information within or referenced in the database, or communications that rely on that information, are truthful and non-misleading, particularly where they are being pointed to in the context of treatment decisions relating to the use of a product for an unapproved use.

The final rule does make a modification to the NPRM regarding applicable clinical trials that are completed before the effective date of the final rule and that study a product that is not approved, licensed, or cleared as of the effective date of the final rule. Proposed § 11.44(a)(2) would have required that for: (1) Applicable clinical trials that reach their completion date prior to the rule's effective date, (2) of products that are unapproved, unlicensed, or uncleared as of the completion date, and (3) for which the studied product is approved, licensed, or cleared by FDA on or after the effective date, if not otherwise subject to other deadlines specified in proposed § 11.44, results information must be submitted *by the earlier of* one year after the completion date or 30 calendar days after FDA approval, licensure, or clearance. A commenter suggested this could result in a situation in which a trial ends shortly before FDA approval or clearance and is not given a full year to submit results information after the trial's primary completion date. This provision has been removed from the final rule. As discussed in more detail below, an applicable clinical trial of an unapproved, unlicensed, or uncleared product that reaches its primary completion date before the effective date of the final rule is not subject either to the results information submission requirements in the final rule or the results information submission requirements specified in section 402(j)(3)(C) and section 402(j)(3)(I) of the PHS Act.

Commenters also suggested changes to the scope of the results information submission requirement for applicable clinical trials of unapproved, unlicensed, or uncleared products and addressed the statutory charge to the Secretary to determine whether the rule should require the submission of results information from applicable clinical trials of unapproved, unlicensed, or uncleared products, whether or not approval, licensure, or clearance will be sought (section 402(j)(3)(D)(ii)(II) of the PHS Act). Commenters suggested various options on the subject of the abandonment of product development, including that abandoned products should be identified, but submission of results information from applicable clinical trials of such products should not be required; commenters also suggested that the rule should only apply to applicable clinical trials of unapproved, unlicensed, or uncleared products that have been declared abandoned by the sponsor.

As explained in the proposed rule and above, while limiting results submission to those applicable clinical trials of unapproved, unlicensed, or uncleared products for which product development has been abandoned by industry would mitigate industry concerns about disclosing potentially valuable information to competitors, it would do little to address concerns about bias in the disclosure of information (79 FR 69577). Considerable information of potential scientific, clinical, and public significance would still be hidden from public view and would continue to be unavailable for consideration by human subjects protection review boards in assessing proposed clinical trials, by individuals considering participation in them, or by other researchers who are planning similar clinical trials or clinical trials of similar products. In addition, limiting results information submission and posting to applicable clinical trials of products for which product development has been abandoned would be difficult to administer because only the sponsor and/or manufacturer are in a position to determine that product development has been abandoned for all potential uses. Moreover, product development is often suspended for periods of time before being resumed when company priorities change or an investigational product is transferred to another company. Information about unapproved, unlicensed, or uncleared products for which product development may have been suspended might therefore remain undisclosed for long periods of time, depriving the public of the benefits that could result from disclosure.

A few commenters suggested that if the proposal is adopted, only a limited number of primary or key secondary outcomes prior to regulatory approval should be required to be submitted, or the final rule should allow the submission of redacted results information, especially when the product has not been approved, licensed, or cleared by FDA. The Agency disagrees; we believe that results information submission for all pre-specified primary and secondary outcomes, as required in the statute, is necessary to serve the public interest in having access to full and complete information. Selective reporting of results information would produce an incomplete and potentially skewed submission that ultimately would not serve the interests of the public and users of ClinicalTrials.gov.

Finally, it was suggested that device manufacturers be permitted to withhold proprietary information from the public as long as doing so does not pose a risk to patients. As discussed in Section IV.B. 5, trials of unapproved or uncleared device products qualify for a delay in the disclosure of registration information. However, based on the evidence available in the published literature as described in Section I of this preamble, we have concluded that selectively withholding of clinical trial information, including results information, at the discretion of the responsible party does not best serve the public interest. In addition, section 402(j) of the PHS Act requires the trial results in summary form (rather than individual participant-level form), which we believe can be provided without disclosing trade secret or confidential commercial information. Commenters did not indicate how such results information is or could be considered proprietary (or how it could contain proprietary information). Furthermore, even if the summary results information required to be submitted and posted does include such proprietary information, as discussed above, section 402(j) of the PHS Act and

this final rule constitute authorization by law to disclose this information.

Final Rule

Based on the comments received and the statutory requirements, this final rule maintains the requirement to submit results information from applicable clinical trials of unapproved, unlicensed, and uncleared products consistent with the timelines outlined in § 11.44. The timely disclosure of results information, along with options for limited delays in results information submission deadlines with certification when seeking initial approval, licensure, or clearance, or approval, licensure, or clearance of a new use, takes into consideration the various interests at stake, including the public health benefits of disclosure and the commercial interests of sponsors.

Registration information must be submitted by the deadlines outlined in § 11.24, which do not distinguish between the submission of information from applicable clinical trials of approved, licensed, or cleared products and information from applicable clinical trials of unapproved, unlicensed, or uncleared products. Section 11.35 specifies (see Section IV.B.5) the timelines for posting of registration information for applicable drug clinical trials (regardless of product approval status), applicable clinical trials of device products that previously were approved or cleared, and applicable clinical trials of device products that have not been previously approved or cleared (which qualify for delayed posting in § 11.35(b)(2)(i)). Section IV.B.5 also describes new § 11.35(b)(2)(ii) that provides a process for a responsible party to indicate to the Director that it is authorizing the Director to publicly post its clinical trial registration information at ClinicalTrials.gov prior to the date of FDA approval or clearance of its device product. If the responsible party submits the Post Prior to U.S. FDA Approval or Clearance data element under § 11.28(a)(2)(i)(Q), the Director will post publicly the registration information that would otherwise be subject to delayed posting as specified in § 11.35(b)(2)(i), except for certain administrative data, as soon as practicable.

Under § 11.44, delayed submission of results information for applicable clinical trials involving products that are unapproved, unlicensed, or uncleared for any use is permitted only if the responsible party certifies as set forth in § 11.44 (c) (and prior to the standard results information submission deadlines as specified in § 11.44(a)) that the sponsor or manufacturer intends to continue with product development, meaning that it is either seeking, or may at a future date seek, initial approval, licensure, or clearance of the product under study in the applicable clinical trial. For the purposes of this final rule only, we interpret ''use'' to include ''indication.'' For the purposes of this final rule, ''indication'' means ''the disease or condition the product is intended to diagnose, treat, prevent, cure, or mitigate.''

Section 402(j)(3)(D)(iv)(III) of the PHS Act directs that, in determining the timeline for submission of results information from applicable clinical trials of unapproved, unlicensed, or uncleared products, the Secretary take into account both the certification process under section 402(j)(3)(E)(iii) of the PHS Act ''when approval, licensure, or clearance is sought'' and ''whether there should be a delay of submission when approval, licensure, or clearance will not be sought.'' Specifically with regard to applicable clinical trials of unapproved, unlicensed, or uncleared products for which approval, licensure, or clearance will not be sought, we interpret the phrase ''will not be sought'' in section 402(j)(3)D)(iv)(III)(bb) of the PHS Act to mean that the sponsor or manufacturer has no intention of continuing with commercial development of the product. For these trials, as with the disclosure of clinical trial results information from applicable clinical trials of all unapproved, unlicensed, or uncleared products, we believe that the public benefits of disclosure of results information outweigh any private, commercial interests (see discussion in Section II, Overview of Statutory Provisions). With respect to products for which initial approval, licensure, or clearance is, or may at a future date be sought, we recognize that, in many cases, this is information that will be known only to the sponsor or manufacturer of the drug product (including biological product) or device product and may not even be known to them at the time a clinical trial is completed, especially for an earlier stage trial, such as a phase 2 applicable drug clinical trial. Instead, the sponsor or manufacturer may know only that it intends to continue with product development, such as through the conduct of a subsequent clinical trial. Therefore, as a condition of delaying results information submission for unapproved, unlicensed, or uncleared products for any use, § 11.44(c) requires the responsible party to certify that the sponsor intends to continue with product development and either is seeking, or may at a future date, seek approval, licensure, or clearance. If the responsible party elects to submit a certification for delayed submission, it is the responsible party's obligation to verify that the particular applicable clinical trial meets the § 11.44(c) criteria, as explained in this preamble.

If, after submission of a certification under § 11.44(c), the drug product (including biological product) or device product studied in the applicable clinical trial becomes approved, licensed, or cleared for the use studied in the applicable clinical trial, results information will be due 30 calendar days after the date of product approval, licensure, or clearance. If, after submission of such a certification, initial approval is no longer being sought (*e.g.,* product development is abandoned), any continued delay in results information submission is not warranted, and the responsible party should submit results information as soon as practicable, but not later than 30 calendar days after the application or premarket notification is withdrawn without resubmission for no less than 210 calendar days (*i.e.,* 240 calendar days after submission of the withdrawal request). We limit the allowable delay period for results information submission for applicable clinical trials of unapproved, unlicensed, or uncleared products for any use to 2 years after the submission of a certification (*i.e.,* up to a total of 3 years after the primary completion date) for delayed results information submission, which parallels the statutorily-mandated 2 year limitation in § 11.44(b). The certification must be submitted prior to the date on which results information would otherwise be due under the standard submission deadline in § 11.44(a) (*i.e.,* 12 months after the primary completion date), and we permit only one certification to be submitted for each clinical trial.

In addition, the final rule maintains § 11.48(a)(6) as proposed in final § 11.48(a)(7), which requires responsible parties to submit additional descriptive results information for applicable device clinical trials of unapproved or uncleared devices for which registration information is not posted at the time of results information submission. In such situations, posting clinical trial results information with certain descriptive information that is similar to the type of information that is included as part of registration, provides the necessary context for understanding clinical trial results information and improves the understanding of posted results information. As explained in the proposed rule, facilitating this

understanding is why journal articles and other reports of the results of clinical trials routinely include information about the disease or condition and interventions under study, the inclusion and exclusion criteria for participants, the location(s) of the trial, etc. Without such information, results data about patient demographics, outcomes, and adverse events could be uninterpretable and inaccessible. For example, patients and other users typically access clinical trial results by searching for (and retrieving) clinical trials with specific characteristics that involve a particular intervention or type of intervention, study a particular disease or condition, recruit certain types of subjects, take place during a particular time period, are conducted in a specific location or particular facility, are sponsored by a particular organization, or match a title or identification number they have found in other public sources.

Similarly, consistent with section 402(j)(3)(D)(i) of the PHS Act, providing information about the purpose of the study, its design, the intervention(s) studied, the types of subjects eligible to participate, the duration of the study, and the outcome measures will enhance the understanding of clinical trial results by researchers, healthcare providers, patients and other users of *ClinicalTrials.gov*. Users can benefit from knowing whether the clinical trial is completed, if data are still being collected for other outcome measures, or if the clinical trial was prematurely terminated. They can benefit from understanding whether information has been submitted for all anticipated outcome measures and corresponds to the outcome measures that the clinical trial was designed to achieve or whether the outcome measures changed during the course of the study. They can also benefit from information to assist in comparing results with the results of other clinical trials and with other publicly available information about a clinical trial of interest and other trials. Whether the clinical trial was reviewed for human subjects protection and who had authority over the conduct of the trial can also be useful. In addition, users may benefit from knowing who submitted the information and when it was last verified (*i.e.,* to indicate whether it might be out of date). Such information is not readily available from information submitted under § 11.48(a)(1)–(5), but is similar to the descriptive information provided during registration (*e.g.,* Primary Purpose, Primary Outcome Measure(s), Overall Recruitment Status) (see § 11.28(a)).

In addition, requiring responsible parties for applicable device clinical trials of unapproved, unlicensed, or uncleared device products to resubmit information submitted previously to the data bank during registration under § 11.28(a), in order to comply with § 11.48(a)(7), would be inefficient and impose an unnecessary burden on responsible parties. It would also introduce the possibility that the additional information provided at the time of results information submission would be inconsistent with the registration information and require the Agency to perform an additional quality review of the registration information. To promote efficiency, responsible parties must fulfill the requirement under § 11.48(a)(7) by affirming in the data bank when submitting clinical trial results information that they are submitting information that is already contained in the data bank and that such information has been updated as specified in § 11.64(a)(iii) and that it will be included as clinical trial results information. Once this affirmation is made, any information listed in § 11.48(a)(7) that was previously submitted to the data bank will automatically populate the results information data fields and be posted when results information is posted.

As discussed in Section IV.B.5 of this preamble, we also note that under final § 11.35(b)(2)(ii), a responsible party can indicate to the Director that it is authorizing the Director to publicly post its clinical trial registration information, that would otherwise be subject to delayed posting, as specified in § 11.35(b)(2)(i), prior to the date of FDA approval or clearance. For an applicable device clinical trial for which registration information described in § 11.28 has been posted in accordance with § 11.35(b)(2)(ii) before the submission of results information described in § 11.48, the requirement of § 11.48(a)(7) will not apply.

C. Submission of Technical and Non-technical Summaries

Overview of Proposal

Sections 402(j)(3)(D)(iii)(I) and (II) of the PHS Act specify that the regulations shall require ''[a] summary of the clinical trial and its results that is written in non-technical, understandable language for patients'' and ''[a] summary . . . that is technical in nature,'' respectively, ''if the Secretary determines that such types of summary [both non-technical and technical] can be included without being misleading or promotional.'' We interpreted this statutory condition to mean that such summaries should be required only if the summaries can be consistently produced by responsible parties in a way that is not misleading or promotional.

In the NPRM, we acknowledged that if non-technical and technical summaries could be consistently produced without being misleading or promotional, patients, members of the general public, clinicians, and researchers might benefit from brief, well-written, accurate, and objective summaries of the results of individual clinical trials (79 FR 69581). We discussed considerations related to the optimal format for narrative non-technical summaries and the question of whether a single, brief summary of an individual trial can provide sufficient background and context to avoid being potentially misleading to a clinician or patient interested in the clinical significance of the results. We described the challenges of producing summaries of trials with many outcome measures and adverse events without being selective. In addition to reviewing the relevant literature on the matter, we consulted with the FDA Risk Communication Advisory Committee [Ref. 72] and considered prior public comments from a public meeting held in 2009 [Ref. 63]. We indicated that, until further research could be conducted to assess the value of these summaries to the public and whether they can consistently be provided in a manner that is objective and not misleading, we would defer the decision about whether or not to require the submission of narrative summaries. We indicated that we would continue to provide links, where possible, from individual clinical trials in *ClinicalTrials.gov* to related peer reviewed literature and other information about the intervention, disease, or condition studied. The NPRM invited public comment pertaining to whether the inclusion of technical and non-technical summaries should be required in clinical trial data submission on *ClinicalTrials.gov* and what methodologies could be employed to ensure non-misleading, non-promotional, accurate, and consistent summaries (79 FR 69582).

Comments and Response

Comments addressed the question of whether the submission of technical and non-technical narrative results summaries should be required. Commenters noted that preparing both technical and non-technical summaries would be burdensome (*e.g.,* a commenter estimated that providing a non-technical summary would add 4 hours to the overall time to complete the

submission of the results information for a clinical trial) and raised concerns regarding the ability of trial sponsors to write accurate, non-promotional, and non-misleading summaries. Commenters suggested that if results summaries were to be required, the Secretary would need to develop and issue guidelines or templates regarding their appropriate authorship, content, evaluation, and format to ensure consistency across summaries. No comments addressed the methods that might be employed to help answer the questions about whether narrative summaries could be consistently produced in a non-promotional and non-misleading manner. However, several commenters suggested external organizations with whom the Secretary might collaborate on narrative summary issues, namely the ICMJE to ensure that narrative summaries would not preclude future journal publications; the Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard to investigate the format they are using for summaries; the FDA regarding Drug Trials Snapshots; and the Patient-Centered Outcomes Research Institute (PCORI) regarding peer review and public release of research findings. One commenter suggested that the summaries could be subject to a peer review process or prepared by independent medical writers. For both technical and non-technical summary results submission, there were commenters who supported deferral of a decision pending further exploration and the development of guidelines for preparing such documents.

With regard to technical summaries specifically, some commenters suggested that such summaries would be redundant to the required trial results information proposed in the NPRM. Other commenters expressed concerns regarding disclosure of proprietary information, particularly if such summaries were to be posted prior to FDA product approval. One commenter supported requiring technical summaries of results because they would suit the needs of professionals, manufacturers, and others in the industry. Several commenters suggested that as an alternative to technical summaries, *ClinicalTrials.gov* could systematically link to published reviews and/or clinical study reports (CSRs) submitted to FDA.

With regard to non-technical summaries specifically, commenters pointed out that it may be difficult for members of the public to understand study results provided in a technical summary and that the provision of lay summaries would enhance public understanding of the results. Others highlighted the difficulty inherent in writing a simple summary that presents the nuances of complex research findings, noting that systematic reviews, which synthesize all available evidence, are better sources of information for the lay public than brief summaries of a single trial. One commenter suggested that the informed consent document could be required in lieu of a lay summary because it provides important basic information in non-technical terms and has been reviewed by an independent party, *i.e.,* an IRB.

Taking the public comments into consideration, and given concerns about the potential for harm to public health from the promotion of medical products for unapproved uses, the Secretary is declining at this time to require narrative results summaries until further research is conducted to determine whether and, if so, how, summaries can be reliably and consistently produced without being promotional or misleading. Current approaches in the dissemination of trial summaries, such as FDA's Drug Trials Snapshots, PCORI's summary reports, and industry efforts to return summary results to participants, may be informative and will be reviewed and considered as part of any further research.

To provide additional information to the general public about a registered clinical trial, we will accept optional submission of the final version of the informed consent document to be posted on the associated record. Although the informed consent document does not provide information on interpreting the results of the trial, the document is written in lay language and its description of the trial's purpose, procedures, risks and potential benefits may help put the trial results into clearer context.

Final Rule

The final rule does not require the submission of technical or non-technical summaries of results to *ClinicalTrials.gov* because we have not identified evidence on the basis of which to conclude that there is a feasible way to ensure that the information contained in such summaries will be consistently produced without being misleading or promotional. We will continue to explore automated ways to consistently produce result summaries in a non-promotional, non-misleading way as well as mechanisms for linking results to information that might assist users in interpreting the results of clinical trials, such as systematic reviews and summary outcome information that sponsors and investigators provide to participants following the trial's completion. Should we determine in the future that narrative summaries can be consistently produced in a non-promotional, non-misleading way, a separate rulemaking process with notice and public comment will be undertaken.

D. Submission of Protocols and Statistical Analysis Plans

Overview of Proposal

Section 402(j)(3)(D)(iii)(III) of the PHS Act stipulates that regulations for an expanded registry and results data bank shall require at the time of results information submission, in addition to basic results information, the submission of ''[t]he full protocol or such information on the protocol for the trial *as may be necessary* to help to evaluate the results of the trial'' (emphasis added).

The NPRM noted that this statutory requirement could be satisfied in several ways, such as ''(1) [r]equiring submission of additional structured data elements derived from, or describing, the protocol; (2) requiring submission of portions of the final protocol or other narrative information about the conduct of the study that is associated with the protocol (*e.g.,* a SAP, if not part of the protocol); or (3) requiring submission of the full protocol at the time of results submission, meaning the final version of the protocol, including all protocol amendments, in a format such as Portable Document Format (PDF)'' (79 FR 69582). As we explained in the NPRM, given the proposals for submission of additional registration and results information, we did not propose to require submission of the protocol or other ''information on the protocol.'' We did, however, solicit public comment on whether the registration and results information proposed for submission was sufficient to meet the statutory requirement. We asked for perspectives on the relative benefits and burdens of preparing and submitting any additional information and how such information would help evaluate the results of the clinical trial.

Comments and Response

Commenters supportive of a requirement for protocol submission maintained that it improves transparency and quality of reporting by providing information to the public about inclusion and exclusion criteria, the interventions studied, and trial outcomes. They suggested that the availability of the protocol allows users to compare reported outcomes and

analyses against those pre-specified in the protocol. Some commenters asserted that a full understanding of the trial results is not possible without having access to the protocol and the trial's procedural details, details they stated permit the study to be replicated or built upon and that are pivotal to improving the design of future trials.

Some commenters pointed to an IOM recommendation that called for sharing of the protocol and SAP not only to help other investigators understand the original analysis, replicate or reproduce the study, and carry out additional analyses, but also because it complements trial registration in identifying trials that were initiated, allows future auditing of data sharing, facilitates meta-analyses and systematic reviews, promotes greater standardization of protocol elements (*e.g.,* interventions, outcomes), and may help reduce unnecessary duplication of studies [Ref. 47].

Another commenter maintained that an added benefit of making protocols available through *ClinicalTrials.gov* was that it would help journal editors, reviewers, and readers verify the a priori or post hoc nature of trial outcomes. They noted that journal editors encounter situations where outcomes reported in manuscripts do not match those listed on *ClinicalTrials.gov* and that posting of study protocols would be an important additional safeguard against reporting bias. Another commenter pointed out that a central archive for protocols would alleviate the burden on clinical trial investigators in addressing multiple requests for a copy of their protocols.

Commenters in support of a requirement for protocol submission also noted that, unless a standardized protocol format were required, the burden would be minimal because the document already exists. One commenter suggested that because the requirement is virtually burden-free and the benefits are so great, the requirement should be retroactive as far back as possible.

Commenters opposed to requiring protocol submission offered a number of reasons for this position. They suggested that the proposed registration and results elements provide sufficient information to understand the results of a clinical trial. Some thought the protocols should not be required because they will be confusing to the public and detrimental to recruitment, noting that they are technical, not standardized, and may have multiple amendments. Some asserted that protocols contain personally identifiable information, proprietary information, or other information that, if publicly disclosed, could be damaging to business interests. They suggested that a submission requirement would conflict with protections under the FD&C Act, FDA regulations, and FOIA. Commenters in support of protocol submission suggested redaction of such information was an appropriate remedy that should be allowed before submission. Finally, other commenters opposed redaction of information based on concerns it would be too burdensome and time consuming, with one commenter suggesting that allowing responsible parties to redact proprietary information might result in the exclusion of essential details needed for others to understand the results of the trial. No specific burden estimates associated with protocol redaction and submission were provided.

We appreciate that the data elements proposed in the NPRM are helpful to those reviewing and analyzing entries in *ClinicalTrials.gov*, and it was due to these additional elements that we did not propose the submission of the protocol in the NPRM. However, we found compelling and persuasive the arguments that protocols provide information in a context that is not captured by these elements alone and that the protocol will improve transparency and the quality of reporting by providing a more complete picture of the trial. We understand that although the registration data elements include descriptors of key features of the protocol, there are times when this additional detail may be helpful to researchers and others with an interest in the clinical trial's results and the ability to assess those results. For example, the protocol provides more detail than the registry and results data elements about methods of participant selection, randomization, masking, and assignment to arms; methods of collecting clinical trial data; specific information about clinical trial interventions (*e.g.,* other elements of care that were provided in addition to the specified interventions); and assessment of adverse events. The protocol may also contain information on the statistical techniques used to analyze collected results information, which helps others in interpreting the submitted results of a clinical trial. The protocol's description of the approach and circumstances that led to data collection may be helpful in contextualizing the submitted results information. We agree that this picture will help users of *ClinicalTrials.gov* to interpret the data elements that are required by this rule and that the protocol will be an important part of results information reporting for those wishing to fully understand the trial and its reported outcome measures.

We were also persuaded by the rationale for protocol submission discussed in the 2015 IOM report on sharing clinical trial data [Ref. 47], which described the value it would have for journal editors, reviewers, and readers in helping to verify trial outcomes and safeguard against reporting bias, and that it would help investigators in addressing multiple individual requests for a copy of their protocols. Further, it would allow for access to this information long after any prevailing document retention requirements have lapsed.

We did not find the argument that some might not understand the protocol to be a sufficient reason to not require its submission. Rather, although we acknowledge that there may be some individuals who may not understand the protocol, we believe that in general it will enhance understanding through its detail, content, and context. Regarding the suggestion that its posting could be detrimental to recruitment, we require the protocol at the time of results information submission, thereby eliminating the concern that posting the protocol will affect a trial's recruitment.

With regard to the argument that the protocol contains proprietary information, section 402(j)(3)(D)(iii)(III) of the PHS Act specifically requires the Agency to determine via this rulemaking whether to require the submission of the protocol. As discussed above in Section III.B, a statute or validly promulgated regulation requiring disclosure constitutes authorization by law to disclose information that might otherwise be considered to be trade secret and/or confidential commercial information as those terms are defined in the FOIA and the TSA. However, notwithstanding this authorization, if there is a case in which a responsible party believes that a protocol does contain trade secret and/or confidential commercial information, the responsible party may redact that information, so long as the redaction does not include any specific information that is otherwise required to be submitted under this rule. For example, the Intervention Name(s) for each intervention studied must be submitted under § 11.28(a)(2)(i)(J); therefore, this information may not be redacted from the protocol for that trial.

The burden of redacting protocols prior to submission is on the responsible party; the Agency does not intend to review protocols to assess

whether they contain trade secret and/or confidential commercial information. Regarding the concern that redaction might result in a protocol lacking in essential details necessary to understand the results, we emphasize that responsible parties must comply with all other applicable results information submission requirements of this rule. The Agency may contact a responsible party if it appears that the responsible party has redacted information that is otherwise required to be submitted under these regulations. More specific guidance regarding redaction will be considered in the future.

In addition, we believe that concerns that might exist about a loss of competitive advantage are mitigated because the submission of the protocol is not required until after the trial is completed and clinical trial results information is submitted in accordance with the deadlines specified in § 11.44. We also note that § 11.44(c) provides for delays in submitting clinical trial results information for an applicable clinical trial that studies a product that is not yet approved by the FDA, thereby allowing for additional time before the protocol is required to be submitted.

Moreover, in our experience, protocols do not contain proprietary information or manufacturer details. However, as noted above, should there be a case in which a protocol does contain such information, redaction of such information will be allowed as long as the redaction does not encompass the information that is otherwise required to be submitted under this rule.

While some commenters were concerned about posting of personal information contained in protocols, in our experience, protocols generally do not contain information about individual clinical trial participants. However, if such information were to be included in a protocol, it should be redacted. Again, the burden of doing so is on the responsible party; the Agency does not intend to review protocols to assess whether they include personal information about trial participants. However, if it comes to the Agency's attention that personal information about trial participants has been included in a protocol, the Agency may contact the responsible party regarding the matter.

Protocols can include information about principal investigators and other individuals associated with conducting a clinical trial. In response to the concerns expressed by the commenters, responsible parties may redact personally identifying information about individuals who are involved in conducting the clinical trial if that information is not otherwise required to be submitted as part of clinical trial information. The Agency anticipates that because information such as work email addresses and contact information related to the clinical trial is likely available through other public sources (*e.g.,* a medical center's Web site), in many cases this information will not need to be redacted and, therefore, the burden associated with redaction will be minimal.

Because the protocol document already exists, we do not foresee this additional submission requirement to be burdensome. Rather, submission of the protocol itself is expected to be a minimally burdensome requirement that would involve an upload of an existing electronic document. We also expect that it will be less burdensome for a responsible party to submit the protocol than to extract and submit specified portions or selected information from a protocol. Similarly, as mentioned above, we do not expect redactions of any proprietary or personal information to be burdensome. The submission of the protocol at the time of the submission of clinical trial results information, rather than at the time of clinical trial registration information, also minimizes the burden on responsible parties in that any amendments that occurred over the course of the trial would already be incorporated into the document.

We also agree with the commenters who urged requiring submission of the SAP if it is not included in the protocol document. Many of the benefits of the protocol that were cited by commenters (summarized above) derived from the statistical analysis section of the protocol. If that section were written as a separate document (the SAP), then that document would be necessary to derive those same benefits (*e.g.,* better understanding of how data were collected and analyzed). As noted by commenters, the IOM recommended that both the full protocol and the SAP, including all versions and amendments, ''should be shared to help other investigators understand the original analysis, replicate or reproduce the study, and carry out additional analysis'' [Ref. 47]. SAPs describe the analyses to be conducted and the statistical methods to be used, including ''plans for analysis of baseline descriptive data and adherence to the intervention, prespecified primary and secondary outcomes, definitions of adverse and serious adverse events, and comparison of these outcomes across interventions for prespecified subgroups. The full SAP describes how each data element was analyzed, what specific statistical method was used for each analysis, and how adjustments were made for testing multiple variables . . . if some analysis methods require critical assumptions, data users will need to understand how those assumptions were verified'' [Ref. 47]. Some commenters objected to requiring the submission of both the protocol and the SAP, for the reasons described above; other commenters raised similar objections specifically with respect to the submission of SAPs. We find these objections unpersuasive for the reasons described above related to protocols. Therefore, we are requiring submission of the SAP as part of clinical trial results information.

If the SAP is submitted as part of the protocol, it need not be separately submitted. Some commenters objected to submission of SAPs because the SAPs might contain proprietary information. Although we think it unlikely that SAPs will contain proprietary information, we will accept redacted SAPs under the same terms as redacted protocols. We wish to emphasize that neither this requirement nor anything in this rule sets standards or creates requirements for the substantive content of protocols or SAPs.

Final Rule

The final rule requires submission of the full version of the protocol and the SAP (if a separate document) as part of clinical trial results information, as specified in § 11.48(a)(5). Submission of the protocol and SAP allows interested users of *ClinicalTrials.gov* to contextualize the reported clinical trial results information. We emphasize that this rule does not create requirements for the substantive content of protocols or SAPs. However, to allow for unambiguous identification of the submitted document(s), the protocol and SAP (if submitted as separate document) must contain a cover page that lists the Official Title (as defined in § 11.10(b)(2)), NCT number (as defined in § 11.10(a), if available), and the date of each document. We are requiring the inclusion of this additional information pursuant to our authority in section 402(j)(3)(D)(iii)(IV) of the PHS Act.

The requirements for submission of the protocol and the SAP are detailed in § 11.48(a)(5) of the final rule, which stipulates that ''[a] copy of the protocol and the statistical analysis plan (if not included in the protocol), including all amendments approved by a human subjects protection review board (if applicable), before the time of submission under this subsection and that apply to all clinical trial Facility

Locations'' must be submitted. It further indicates that ''[t]he responsible party must include the Official Title (as defined in § 11.10(b)(2)), NCT number (as defined in § 11.10(a)) (if available), and date of the protocol and the statistical analysis plan on the cover page of each document.'' In addition, ''[t]he responsible party may redact names, addresses, and other personally identifiable information, as well as any trade secret and/or confidential commercial information (as those terms are defined in the Freedom of Information Act (5 U.S.C. 552) and the Trade Secrets Act (18 U.S.C. 1905)) contained in the protocol or statistical analysis plan prior to submission, unless such information is otherwise required to be submitted under this part. The protocol and statistical analysis plan must be submitted in a common electronic document format specified at *https://prsinfo.clinicaltrials.gov.''*

The protocol and, if separate, the SAP, will be posted with other clinical trial results information, in accordance with § 11.52. If amendments are made to the protocol between the initial submission of partial clinical trial results information and later submission of additional partial results information, the responsible party must submit a copy of the revised protocol at the time of the later submission of partial results information, in accordance with § 11.44(d)(3)(i). However, the Protocol and Statistical Analysis Plan results data element in § 11.48(a)(5) are excluded from the updating requirements in § 11.64(a)(2)(i). Each submitted version of the protocol and SAP will continue to be available through the *ClinicalTrials.gov* archive site.

IV. Discussion of Public Comments Related to Specific Provisions of the Regulations

A. Subpart A—General Provisions

1. 11.2—What is the purpose of this part?

Overview of Proposal

The NPRM described in § 11.2 the overall purpose of the regulations. Implementing section 402(j) of the PHS Act (42 U.S.C. 282(j)), the rule provides the requirements and procedures for the submission of clinical trial information for certain applicable clinical trials and other clinical trials to the Director of the NIH to be made publicly available through *ClinicalTrials.gov*.

Comments and Response

As noted earlier, more than half of the submitted comments were identical in content. These commenters addressed proposed § 11.2 by recommending that the final rule be expanded to require registration and results information submission for all clinical trials. They reasoned that it was important and in the public interest for data on all clinical trials of drugs, biological products, and devices, and not only ''certain applicable clinical trials,'' to be posted before the trial moves from one phase to the next. These commenters also suggested replacing the phrase ''certain applicable clinical trials'' in proposed § 11.2 with ''all clinical trials.''

The statute required the Agency to make a number of decisions through rulemaking, including whether to expand the requirement to report results information to applicable clinical trials of unapproved, unlicensed, or uncleared products, but it did not call for consideration of whether all clinical trials should be subject to registration and reporting requirements. Since the statute limits the applicability to applicable clinical trials as defined, these comments are outside the scope of the current rulemaking. Comments on the scope of the rule are further discussed in Section III.A of this preamble, Scope and Applicability, and in Section IV.B.2 in the discussion of § 11.22.

Final Rule

No changes are made in § 11.2 of the final rule.

2. 11.4—To whom does this part apply?

Overview of Proposal

Proposed § 11.4(a) specified that the regulations would apply to any person or entity that is considered to be the ''responsible party,'' defined in section 402(j)(1)(A)(ix) of the PHS Act, for an applicable clinical trial that is required to be registered under § 11.22 or a clinical trial for which clinical trial information is submitted voluntarily under § 11.60. Proposed § 11.4(b), which would implement section 402(j)(1)(B) of the PHS Act, required the responsible party to communicate their identity and contact information to the Director by submitting the Responsible Party Contact Information data element during registration. Proposed § 11.4(c) outlined procedures for determining the responsible party for each applicable clinical trial or other clinical trial subject to this part. In particular, § 11.4(c)(1) specified who would be considered the sponsor and required that each applicable clinical trial or other clinical trial must have one sponsor. Furthermore, § 11.4(c)(2) established the requirements and procedures for a sponsor to designate a principal investigator to be the responsible party. If and when a designated principal investigator becomes unable to meet all of the requirements for being designated as a responsible party, proposed § 11.4(c)(3) outlined the mechanisms by which the sponsor would become the responsible party.

Comments and Response

Commenters suggested replacing the phrase ''applicable clinical trial'' in proposed § 11.4 with ''all clinical trials.'' Commenters also expressed their opinions regarding proposed § 11.4 which focused on the designation of a responsible party. While commenters expressed support for assigning one responsible party per applicable clinical trial, they sought clarification regarding procedures for when a designated responsible party becomes unable to meet all of the requirements under § 11.4(c)(2)(i) (*e.g.,* principal investigator leaves the institution, principal investigator dies). Furthermore, a commenter suggested that the responsible party remain responsible for clinical trial information submission requirements even after leaving his/her institution and another suggested that the responsible party be able to change the sponsor, for example, when the principal investigator changes institutions.

As explained in the response to comments for § 11.2, section 402(j) of the PHS Act did not call for consideration of whether all clinical trials should be subject to registration and results information reporting requirements, and it limits the applicability to applicable clinical trials as defined. The Agency outlines in § 11.4(c)(2) and (3) of the final rule the procedures on the designation of a responsible party. These procedures specify that in the event a principal investigator who has been designated the responsible party no longer meets or is no longer able to meet all the requirements of § 11.4(c)(2)(i), the sponsor must withdraw the designation in the format specified at *https://prsinfo.clinicaltrials.gov* (or successor site), at which time the sponsor will be considered the responsible party unless and until the sponsor makes a new designation. These procedures, however, do not allow for a principal investigator who has been designated as the responsible party to change the sponsor because § 11.4(c) defines the sponsor as the default responsible party. Consistent with the statute, the sponsor is permitted to designate a principal

investigator as the responsible party. However, if the designated principal investigator no longer meets or is no longer able to meet the criteria for being designated a responsible party (*e.g.,* due to changing institutions), the role of responsible party reverts back to the original sponsor.

Commenters also suggested that it would be more helpful if the electronic *ClinicalTrials.gov* system, *i.e.,* PRS, used by responsible parties to register and submit results information for their trials included a way for sponsors to designate a principal investigator as the responsible party. Commenters also suggested that PRS administrators should be allowed to control the settings in the Responsible Party field so they can set the ''default'' according to policies or preferences established by an institution.

Sponsors are not only responsible for assigning the role of responsible party, but they must also ensure that a designated principal investigator knows that he/she has been assigned the responsibility and has accepted the role and designation. Given the legal ramifications of the responsible party role, we do not believe it is appropriate for the assignment to be set through a default mechanism controlled through the PRS. We note that tools are available in the PRS to help remind responsible parties, including principal investigators designated as a responsible party, when a study record requires attention (see *https://prsinfo.clinicaltrials.gov* or successor site). We will continue to evaluate and develop tools in the PRS to help ensure that responsible parties understand their reporting obligations.

Final Rule

Final § 11.4 maintains the proposed approach of the NPRM, and clarifies in § 11.4(a) that the rule also applies to any responsible party required by the Director to register under § 11.62 to protect the public health (discussed in more detail in Section IV.D.2). Thus, final § 11.4(a) specifies that the rule applies to the responsible party for an applicable clinical trial that is required to be registered under § 11.22, for which clinical trial information is voluntarily submitted under § 11.60 (discussed in more detail in in Section IV.D.1), or for which the Director has determined, consistent with § 11.62, that clinical trial information must be submitted in order to protect the public health. The responsible party is either the sponsor of the clinical trial or a principal investigator who meets the criteria specified in § 11.4(c)(2) and has been so designated by the sponsor. In no case will this rule apply to the sponsor or principal investigator or other individual or entity associated with a clinical trial of drug or device not subject to FDA jurisdiction. Although section 402(j)(4)(A) of the PHS Act directs the Secretary to permit ''[v]oluntary submissions'' of clinical trial information for ''a clinical trial that is not an applicable clinical trial or that is an applicable clinical trial that is not subject to'' the registration provisions of section 402(j)(2) of the PHS Act, we interpret section 402(j) of the PHS Act and, thus, the final rule as not applying to anyone who submits information to *ClinicalTrials.gov* about trials of interventions that are not subject to FDA jurisdiction under sections 505, 510(k), 515, 520(m), or 522 of the FD&C Act, or section 351 of the PHS Act. Moreover, we interpret section 402(j) of the PHS Act as not applying to anyone who submits information to *ClinicalTrials.gov* for a study that is neither an applicable clinical trial (including a pediatric postmarket surveillance of a device product as defined in this part) nor a clinical trial as defined in § 11.10(a), even if it involves a drug or device subject to sections 505, 510(k), 515, 520(m), or 522 of the FD&C Act, or section 351 of the PHS Act. For example, section 402(j) of the PHS Act would not apply to information submitted for a study using a diagnostic tool that is a device product subject to section 510(k) of the FD&C Act, such as a magnetic resonance imaging scanner, that is not studying the device product and is not otherwise an applicable clinical trial, clinical trial as defined in § 11.10(a), or pediatric postmarket surveillance of a device product as defined in this part. (See the discussion of ''Studies a U.S. FDA-regulated Device Product'' in Section IV.B.4) Consistent with other statutory authorities of the Agency and long-standing practice, however, *ClinicalTrials.gov* may, and does, accept registration and results information on clinical studies, as defined in § 11.10(a), that are not subject to the requirements of section 402(j) of the PHS Act (including under this rule).

Section 11.4(b) of the final rule implements section 402(j)(1)(B) of the PHS Act, which provides that the Secretary ''shall develop a mechanism by which the responsible party for each applicable clinical trial shall submit the identity and contact information of such responsible party to the Secretary at the time of submission of clinical trial [registration] information.'' Section 11.4(b) provides that the responsible party's identity and contact information must be included as part of the clinical trial information that is submitted in accordance with § 11.28(a)(2)(iii)(B) and § 11.28(a)(2)(iv)(F) and updated in accordance with § 11.64(a). Responsible party contact information must be provided under the data element entitled Responsible Party Contact Information (§ 11.28(a)(2)(iv)(F)) that, as specified in § 11.10(b)(37) includes the name, official title, organizational affiliation, physical address (*i.e.,* street address), mailing address, phone number, and email address of the responsible party or of a designated employee of the organization that is the responsible party.

Section 11.4(c) outlines procedures for determining the responsible party for each clinical trial subject to this part. The Agency believes that there must be one (and only one) responsible party for each clinical trial subject to this part for which clinical trial information is submitted. Having only one responsible party for each clinical trial facilitates procedural requirements during registration and results information submission and prevents situations in which both a sponsor and a principal investigator consider themselves the responsible party and submit information for the same clinical trial. Absent a responsible party, the objectives of registration and results information submission cannot be met. The definition of responsible party under section 402(j)(1)(A)(ix) of the PHS Act specifies, first, that the sponsor will be the responsible party and, second, that the principal investigator is the responsible party if delegated this role through a designation ''by a sponsor, grantee, contractor, or awardee.'' With regard to clinical trials, the Agency looks first to determine who is the sponsor of the clinical trial, consistent with the definition in this part, and assumes that such individual or entity is the responsible party, unless the principal investigator has been designated the responsible party in accordance with the procedure in § 11.4(c)(2). For a pediatric postmarket surveillance of a device product that is not a clinical trial, the responsible party would be considered the entity FDA, under section 522 of the FD&C Act, orders to conduct the pediatric postmarket surveillance of a device product. In the final rule, § 11.4(c) clarifies that ''device'' means ''device product.''

Section 11.4(c)(1) specifies who will be considered the sponsor. The Agency believes that there must be a sponsor as that term is used in section 402(j)(1)(A)(ix) of the PHS Act for each clinical trial and that (as stated above)

there can be only one sponsor. Without a defined sponsor, there cannot be a responsible party for a clinical trial because the responsible party is defined as either the sponsor or the principal investigator who has been so designated by the sponsor. The definition of sponsor in § 11.10(a) includes both a ''sponsor'' and a ''sponsor-investigator'' as those terms are defined in 21 Code of Federal Regulations (CFR) 50.3. or any successor regulation. Both definitions in 21 CFR 50.3 refer to the sponsor as, in part, the person or entity who ''initiates'' the clinical investigation. For purposes of this rule, if a clinical trial is being conducted under an IND or investigational device exemption (IDE), the IND/IDE holder is considered to be the individual or entity who initiated the clinical trial and, therefore, the sponsor, regardless of how the clinical trial is being funded. For clinical trials not conducted under an IND or IDE, the sponsor is considered to be the person or entity who initiated the trial and would be identified as follows:

(1) Where the clinical trial is being conducted by an entity under a research assistance funding agreement such as a grant or sponsored research agreement, the funding recipient generally is considered to be the initiator of the clinical trial, and therefore, the sponsor. This is because, as a general rule, when a clinical trial is funded in this manner, the funding recipient ''initiates'' the clinical trial process by, for example, submitting a funding proposal and designing the clinical trial.

(2) Where the clinical trial is being conducted by an entity under a procurement funding agreement such as a contract, the party obtaining the goods or services for its direct benefit or use (the funder) generally is considered to be the initiator of the trial, and therefore, the sponsor. This is because, as a general rule, when a clinical trial is funded in this manner, it is the funder of the clinical trial that initiates the clinical trial process by, for example, contracting with another entity for that entity to conduct a clinical trial meeting the specifications of the funder.

(3) Where there is no funding agreement supporting the clinical trial, the person or entity who initiated the clinical trial by preparing and/or planning the clinical trial, and who has appropriate authority and control over the clinical trial to carry out the responsibilities under section 402(j) of the PHS Act (including this part) is the sponsor.

Furthermore, § 11.4(c)(2) establishes the procedures for designation of a principal investigator as the responsible party. Section 402(j)(1)(A)(ix) of the PHS Act defines the responsible party, as either ''the sponsor of the clinical trial'' (as defined in [21 CFR 50.3] (or any successor regulation)); or the principal investigator of such clinical trial if so designated by a sponsor, grantee, contractor, or awardee,'' so long as such person meets certain criteria. In order to give practical effect to this provision, we conclude that, for any given applicable clinical trial or other clinical trial subject to this part, only one entity—the sponsor—can designate the principal investigator as the responsible party. We believe this interpretation is consistent with section 402(j) of the PHS Act because in many situations the sponsor of the clinical trial will also be a grantee, contractor, or awardee. In addition, interpreting this provision in a different manner could result in situations in which both a sponsor (*e.g.,* an IND/IDE holder) and a principal investigator (designated by a separate grantee, contractor, or awardee) consider themselves the responsible party and submit information for the same clinical trial. This would not only increase the overall burden associated with registration, but more importantly would undermine the integrity of the data bank and potentially cause confusion to users of the system.

Section 402(j)(1)(A)(ix) of the PHS Act permits a principal investigator to serve as a responsible party only if he or she ''is responsible for conducting the trial, has access to and control over the data from the clinical trial, has the right to publish the results of the trial, and has the ability to meet all of the requirements under [section 402(j) of the PHS Act] for the submission of clinical trial information.'' Accordingly, if the principal investigator does not meet the specified conditions for serving as the responsible party, the sponsor cannot designate the principal investigator as the responsible party, and the sponsor must remain the responsible party. In § 11.10(a) we define, for purposes of this part, the term principal investigator to mean ''the individual who is responsible for the overall scientific and technical direction of the study.'' We note that under section 402(j)(1)(A)(ix) of the PHS Act, in order to be designated the responsible party, the principal investigator must be responsible for ''conducting the trial'' and must have ''access to and control over the data from the clinical trial.'' We interpret ''the trial'' to refer to the ''clinical investigation'' as defined in 21 CFR 312.3 and this part, and to mean ''the entire clinical investigation.'' Similarly, we interpret ''the data'' to mean ''all of the data,'' including data collected at all sites of a multi-site trial.

To clarify our understanding of section 402(j)(3)(C)(iv) of the PHS Act as it relates to whether a principal investigator would be eligible to serve as the responsible party, this section requires the responsible party to indicate, as an element of clinical trial results information, whether there exist ''certain agreements,'' which are described, with certain exceptions, as ''an agreement . . . that restricts in any manner the ability of the principal investigator, after the completion date of the trial, to discuss the results of the trial at a scientific meeting or any other public or private forum, or to publish in a scientific or academic journal information concerning the results of the trial.'' We do not view the presence of such an agreement as necessarily disqualifying a principal investigator from serving as the responsible party. Rather, we view only those agreements that prevent the principal investigator from performing the functions described in section 402(j)(1)(A)(ix)(II) of the PHS Act and § 11.4(c)(2)(i) of this part or from submitting clinical trial information or any updates to such information required by section 402(j) of the PHS Act and this part as preventing the principal investigator from serving as the responsible party.

To provide for the orderly implementation of section 402(j)(1)(A)(ix)(II) of the PHS Act, pursuant to which the sponsor may designate a principal investigator as the responsible party, and ensure that the principal investigator has notice of the designation, we have detailed the process in § 11.4(c)(2)(ii) for designating a principal investigator. It indicates that the sponsor shall provide notice of the designation to the principal investigator and obtain acknowledgement of the principal investigator's understanding of their responsibilities under this part. We intend to continue to provide mechanisms in the PRS for the sponsor and the principal investigator to indicate the designation and the acknowledgement, respectively. The designation by the sponsor is currently reflected in *ClinicalTrials.gov* by having the principal investigator submit clinical trial information via the sponsor's organizational account (the sponsor must provide an account for the principal investigator within the sponsor's PRS organizational account). The acknowledgement is reflected by having the principal investigator list their name as the responsible party and indicate that they were designated as the responsible party by the sponsor.

This approach has been available in *ClinicalTrials.gov* since 2011.

If and when a designated principal investigator no longer meets or is no longer able to meet all of the requirements of a responsible party, § 11.4(c)(3) outlines the mechanisms by which, if the withdrawal of such designation occurs, the sponsor would become the responsible party. This might occur if, for example, a principal investigator dies, retires, changes jobs, or turns control of the clinical trial data over to the sponsor. Final § 11.4 modifies the NPRM approach by clarifying in § 11.4(c)(3) that the sponsor, and not the clinical investigator, must withdraw the designation of a principal investigator as the responsible party. Because of this clarification, proposed § 11.4(c)(3)(ii) is no longer necessary, so § 11.4(c)(3)(i) is designated as § 11.4(c)(3).

We note that even if a sponsor designates a principal investigator as the responsible party for an applicable clinical trial registered under § 11.22, there may be times when the sponsor would need to provide the principal investigator with certain information in order for the principal investigator to meet the obligations of the responsible party. For example, in order for a principal investigator who has been designated as the responsible party to satisfy the conditions for submitting a certification for delayed submission of results information under § 11.44(b) or (c), the sponsor would likely have to provide the investigator with information about the conditions involving FDA action on a product application or submission, such as approval, that would require the responsible party to submit clinical trial results information as set forth in § 11.44(b) or (c).

Although we expect that a principal investigator who has been designated as the responsible party to request such information from the sponsor, we also expect a sponsor who has designated a principal investigator as the responsible party to provide appropriate information in a timely fashion. A principal investigator who is not provided the information necessary to enable him or her to meet all of the requirements for submitting and updating clinical trial information does not meet the criteria set forth in § 11.4(c)(2)(i) to serve as the responsible party. If the sponsor does not provide the principal investigator with the requisite information to meet the criteria under § 11.4(c)(2)(i), the principal investigator cannot be designated, or continue to act, as a responsible party and the responsible party would be, or would revert to, the sponsor.

3. 11.6—What are the requirements for the submission of truthful information?

Overview of Proposal

Section 402(j)(5)(D) of the PHS Act specifies that ''clinical trial information submitted by a responsible party under this subsection shall not be false or misleading in any particular.'' In addition, the NPRM described other federal laws that address the submission of false or misleading information to the Federal Government (79 FR 69597). Specifically, it is a prohibited act under section 301(jj)(3) of the FD&C Act to submit clinical trial information under section 402(j) of the PHS Act that is false or misleading in any particular. In addition, other federal laws govern the veracity of information submitted to the Federal Government, such as 18 U.S.C. 1001 (making it a crime to make certain false statements to the executive, legislative, or judicial branch of the U.S. Government).

Proposed § 11.6 set out the requirements for the submission of truthful information. Proposed § 11.6(a) stated that submitted clinical trial information must not be false or misleading and that submission of such information may subject the responsible party to civil or criminal liability. Proposed § 11.6(b) required the responsible party to certify that submitted information is truthful and not misleading and that the responsible party is aware of the potential consequences of submitting such information. The certification was intended to ensure that responsible parties are aware of these statutory requirements and to provide an opportunity for them to attest to the veracity of the information at the time of submission.

Comments and Response

Commenters addressed proposed § 11.6. While no commenters disagreed with the proposal to include an explicit requirement that submitted clinical trial information must not be false or misleading and that a warning that submission of such information would subject the responsible party to civil, criminal, and/or administrative liability, commenters did address the proposal to require responsible parties to certify that submitted information is truthful and not misleading and that the responsible party is aware of the potential consequences of submitting such information. Several commenters noted that Title VIII of FDAAA did not stipulate that the Agency should require such a certification in the context of submissions to *ClinicalTrials.gov.* They also suggested that the requirement effectively duplicated three other statutory requirements beginning with two provisions in Title VIII of FDAAA that require the information submitted to *ClinicalTrials.gov* to not be false or misleading (section 282(j)(5)(D) of the PHS Act), which is reflected in proposed § 11.6(a) and the requirement that sponsors submit a certification to accompany the product applications or submission to FDA stating that the sponsor is in compliance with Title VIII of FDAAA (section 282(j)(5)(B) of the PHS Act), and reflected in the prohibited acts provisions (21 U.S.C. 331(jj)(3). They also pointed to the statutory prohibition on making false statements to the Federal Government at 18 U.S.C. 1001, which carries criminal penalties.

One commenter questioned the appropriateness of requiring responsible parties to certify that information submitted is not misleading due to a concern about how members of the public might react to the information. The concern was related to the fact that the structured nature of the database limited the responsible party's ability to provide clarifying contextual information, which if allowed to be provided, in the view of the commenter, would minimize the possibility of misleading a reader about some aspect of the clinical trial. The commenter also suggested that the proposed certification requirement would require a responsible party to evaluate whether providing the submitted information could ''mislead'' a member of the public and that, if the responsible party concluded that such a result were even remotely possible, they would be in an untenable position of having to reconcile conflicting legal obligations (*i.e.,* the responsible party could not satisfy its legal obligation to submit the clinical trial information under the PHS Act without certifying otherwise).

Commenters suggested alternatives to the certification requirement. One suggested that the requirement be reworked to focus on assuring that the submitted information is ''truthful and complete'' rather than the subjective ''not misleading.'' Another suggested that it would be more appropriate to require the responsible party to certify that ''the information contained in this submission is accurate to the best of the sponsor's knowledge.'' Notwithstanding the general support expressed for § 11.6, and although we do not agree that providing structured data entry in standard data formats could lead to misinterpretations of the data, we

conclude that the commenters who addressed proposed § 11.6(b) specifically raised some valid concerns. The commenters suggested that responsible parties are well aware that they are legally bound to submit truthful information to the Federal Government and that a specific attestation to the veracity of the information at the time of information submission to *ClinicalTrials.gov* is unnecessary. As such, and given the other provisions in section 402(j) of the PHS Act that protect against the submission of false or misleading information, we have decided to drop the requirement that the responsible party certify that submitted information is truthful and not misleading and that the responsible party is aware of the potential consequences of submitting such information. With regard to the hypothetical concern that providing structured data entry in standard data formats could lead to misinterpretations of the data, it is important to note that we are not aware that such misunderstandings have occurred nor did any comments identify a specific example. Section 11.6(a) will be retained as a stand-alone provision of the final rule.

Final Rule

The final rule eliminates proposed § 11.6(b) and retains the requirement that submitted clinical trial information must not be false or misleading. The final rule also clarifies in § 11.6 that a responsible party who submits false and/or misleading information may be subject to civil monetary penalties and/or to other civil or criminal remedies available under U.S. law. Eliminating proposed § 11.6(b) does not change the responsible party's obligation to be truthful and not misleading in submissions to *ClinicalTrials.gov.*

4. 11.8—In what format must clinical trial information be submitted?

Overview of Proposal

Section 402(j)(3)(D)(v)(I) of the PHS Act requires the establishment of a ''standard format'' for the submission of clinical trial information. Section 402(j)(2)(B) of the PHS Act also requires that clinical trial information be submitted in such a way that is searchable by the public. Proposed § 11.8 set forth the required format for submitting clinical trial information to *ClinicalTrials.gov.* The proposal specified that information must be submitted electronically to *ClinicalTrials.gov* in the format specified at *http://prsinfo.clinicaltrials.gov* and explained that no other format would be accepted. Although the proposal used the phrase ''form and manner'' instead of ''format,'' we are using ''format'' in the final rule to be consistent with the language of the statute in section 402(j)(3)(D)(v)(I). As discussed in sections II.B and III.C.10 of the NPRM, NLM is adopting a tabular, structured data entry system to promote objective reporting, optimize data display, permit effective searching of *ClinicalTrials.gov,* and facilitate cross-trial comparisons.

Proposed §§ 11.10, 11.28, and 11.48 specified the individual data elements of clinical trial information that must be submitted to *ClinicalTrials.gov* at the time of registration and results information submission (and updated in accordance with proposed § 11.64), including the subelements that are considered to be part of a data element (*e.g.,* proposed § 11.10(b)(5) specifies that the Study Design data element includes the subelements Interventional Study Model, Number of Arms, Arm Information, Allocation, Masking, and Single Arm Controlled).

In sections IV.B.4 and IV.C.4 of the NPRM, we described the specific format in which data elements and subelements would be required to be submitted to *ClinicalTrials.gov.* For some data elements and subelements, responsible parties would be required to submit information in free-text form. For other data elements and subelements, responsible parties would be required to select the best response from menus of options presented in *ClinicalTrials.gov.* The Agency also developed a mechanism for uploading registration and results data in an automated electronic fashion using eXtensible Markup Language (XML) files.

We explained in the NPRM preamble that the Agency might make minor changes from time to time to the specific format in which responsible parties would be required to submit individual data elements and subelements to *ClinicalTrials.gov* (79 FR 69598). We indicated that we would provide prior notice and seek public comment on any proposed changes to the format of submitting clinical trial information and that any changes would ultimately be reflected in the PRS.

We invited comment on the specific format described in the proposed rule for submitting data elements and subelements of proposed clinical trial information, including comments on the benefits and burden associated with providing proposed data elements and subelements, whether proposed menu options are sufficient to accommodate the range of potential entries (*e.g.,* for different trial designs), and whether an ''other'' option is needed in additional data elements (79 FR 69598). We also invited comment on the proposed approach described in this section for modifying the format of submitting clinical trial information over time.

Comments and Response

Commenters addressed the proposed format of submission. Some comments explicitly supported the proposed rule requirements for information to be submitted in a structured format. Other comments addressed data formatting issues in the PRS. Some of these commenters recommended that the PRS allow submissions in Microsoft Excel® files, such as for adverse events, particularly because academic medical centers are generally not familiar with XML. We note that the PRS system has allowed for the submission of adverse event information in spreadsheet format, including Excel, since 2013 and will continue to allow this format.

Other commenters requested that the PRS accept submissions in the same electronic formats as required by the Agency and other federal funders for submissions to their own databases (*e.g.,* Clinical Trial Reporting Program (CTRP) for the National Cancer Institute (NCI)). This approach of broadly accepting the same electronic format as other systems is not feasible. Any single standard data format adopted by *ClinicalTrials.gov* must provide sufficient generality and flexibility to accommodate accurate reporting of the mandated clinical trial information for a wide range of clinical trial designs, research areas/domains, and funder/sponsor classes covered by the law. While the Agency appreciates that accepting a variety of submission formats from other federal databases may be less burdensome for responsible parties, the PHS Act requires the final rule to establish a standard format for the submission of clinical trial information. This standard format will, in turn, facilitate search and comparison of entries in the registry data bank, as is also required under the statute. Furthermore, it is possible for other systems to map their content to the standard data format at *ClinicalTrials.gov.* For example, because the data elements used to describe a clinical trial in the NCI's CTRP are designed to be compatible with the standard format required for submitting clinical trial registration information to *ClinicalTrials.gov,* responsible parties who have previously submitted trial information to CTRP can submit that same information directly into the PRS at *ClinicalTrials.gov.* NCI intends to continue to ensure that the information

collected in CTRP is compatible with the requirements of the final rule, while continuing to collect and maintain other information that meets distinct CTRP purposes. NIH is also taking steps to bring more standardization to the information obtained from clinical trial applicants and awardees in order to enhance its stewardship of clinical trials. These efforts will also take into consideration the data elements in *ClinicalTrials.gov.*

ClinicalTrials.gov supports this information exchange by making available to all organizations the specific data elements and their definitions, an XML schema, an application program interface (API), and information about validation messages. We, therefore, retain the PRS submission format in the final rule in order to meet the requirements of the law, but will continue to allow responsible parties who have previously submitted clinical trial data elements to a number of other databases that are compatible with the PRS standard format to transfer clinical trial information automatically from those databases into *ClinicalTrials.gov.*

Some commenters recommended the use of the Clinical Data Interchange Standards Consortium (CDISC) data format to ensure harmonization for registration and results information reporting. To our knowledge, there is no existing standard data format that supports the entirety of the requirements in the final rule. However, if such a standard data format is developed and adopted by a significant number of responsible parties, the Agency will work to provide appropriate interfaces for providing information in that format. In general, the PRS will accept XMLs that meet the requirements of the PRS and that include information that satisfies the elements and subelements required in this regulation.

A number of commenters also stressed the importance of harmonization with international and other standard data formats for uniformity in registration and results information submissions. Some commenters requested that data formats be made consistent and be harmonized with databases such as the EU EudraCT database administered by the EMA [Ref. 70], or the WHO International Clinical Trial Registry Platform Trial Registration Data Set (Version 1.2.1) [Ref. 73]. One commenter requested specifically that any new data technologies and database functionalities should be consistent with the EU and other registration databases.

We note that the NPRM preamble identified data elements that are consistent with the WHO Trial Registration Data Set (*i.e.,* brief title, official title, study design, primary disease or condition being studied in the trial, focus of the study, intervention name, primary and secondary outcome measures, eligibility criteria, overall recruitment status, and secondary identifications (IDs)) (79 FR 69611 et al). These data elements are maintained in the final rule. In addition, the Agency provided technical assistance to the EMA during development of the EudraCT results database so that EudraCT's data requirements are substantially aligned with the requirements for *ClinicalTrials.gov* [Ref. 71]. Also, in April 2015, WHO issued a Statement on Public Disclosure on Clinical Trial Results [Ref. 74]. Although section 402(j)(3)(D)(vi) of the PHS Act requires the Agency to consider the status of consensus data elements set of the WHO for reporting clinical trial results information, the WHO's April 2015 statement did not include any consensus data elements. The Agency notes that opportunities to incorporate newer data formats in the future will be available through the procedures described for format changes in the section below.

One commenter requested that the Systematized Nomenclature of Medicine—Clinical Terms (SNOMED CT®) be used for terminology, or in the alternative ICD–10, to ensure the standard's ability to ''map'' to electronic health records. SNOMED CT® is a comprehensive clinical terminology owned, maintained, and distributed by the International Health Terminology Standards Development Organization [Ref. 75], which includes NLM as the U.S. member. SNOMED CT® is used in systems of the Federal Government for the electronic exchange of clinical health information and is a required standard data format in interoperability specifications of the U.S. Healthcare Information Technology Standards Panel [Ref. 76]. Since SNOMED CT® provides clinical terminology, it applies most directly to the data element of ''primary disease or condition being studied in the trial, or focus of the study'' (§ 11.10(b)(9)). We note that the rule allows the use of SNOMED CT® for this data element or any other vocabulary that has been mapped to Medical Subject Headings (MeSH®) [Ref. 77] with the Unified Medical Language System (UMLS) Metathesaurus. The use of ONC-certified or endorsed terminologies is encouraged where possible, including, but not limited, to SNOMED CT and Logical Observation Identifiers Names and Codes, known by its acronym LOINC®.

Finally, some comments requested that an ''Other'' category option be provided for all data elements. We have instead included an ''Other'' category as menu options only for those data elements where we believe it is necessary and appropriate. In some instances, such as for Study Phase and Study Type, the menu list is comprehensive and no ''Other'' category is needed. An advantage of providing a comprehensive list of substantive options, when possible, is to mitigate confusion and potential errors during data entry. Another key advantage of using only controlled terms as menu items is that it increases structure of the database, thereby facilitating accurate search and complete information retrieval. Allowing the selection of an ''Other'' option with additional free-text elaboration can limit the specificity and searchability of the database. Thus, we have limited the number of data elements that provide an ''Other'' category as an option. As the nature of clinical research methodologies and practices evolve and we gain more experience with certain data elements, we anticipate that menu options will likely change. As described in more detail in the final rule discussion for § 11.8, we will use a notice-and-comment process before adding any new menu options for a data element.

Final Rule

The final rule maintains § 11.8, with some modification for further clarity, in requiring ''Information submitted under this part must be submitted electronically to *ClinicalTrials.gov,* in the format specified at *https://prsinfo.clinicaltrials.gov.*'' The final rule also modifies in the section title the phrase ''form and manner'' to ''format'' to be consistent with the language used in section 402(j)(3)(D)(v)(I) of the PHS Act.

This final rule also specifies the data elements and subelements defined in § 11.10 and required by § 11.28 and § 11.48. In addition, by describing the registration and results information to be submitted to *ClinicalTrials.gov,* this final rule preamble specifies the format in which information will be submitted (such as free text or menu selections). The format specified in this final rule preamble will be described at *https://prsinfo.clinicaltrials.gov* (or successor site). The choice of providing menu options versus free-text fields and the set of menu options offered for specific data elements and subelements are

based on our experience in operating *ClinicalTrials.gov* and on comments received from users of *ClinicalTrials.gov,* including those who commented on the FDA draft and final guidance documents that were issued in 2002 and 2004 [Ref. 78, 79] (79 FR 69570) and the preliminary version of the results database and adverse event module that were available for testing beginning in the spring of 2008 (73 FR 29525). Some menus offer a fixed set of options without an ''Other'' option; others offer a prespecified set of options plus an ''Other'' option. In most cases, responsible parties selecting the ''Other'' option would be required to provide a free-text response to elaborate on the ''Other'' selections. Some data elements without an ''Other'' option also include an optional free-text field in which responsible parties could voluntarily provide additional information about the option selected.

The use of menu options is intended to promote the entry of data in a structured format that allows users to search *ClinicalTrials.gov* and retrieve comparable information, consistent with the requirements of sections 402(j)(2)(B) and (3)(D)(v)(I) of the PHS Act. Menu options have been used in *ClinicalTrials.gov* since its launch and are routinely used to improve the quality and to help ensure the completeness of data submitted to information systems. Their use can reduce typographical errors in data entry and minimize the data entry burden on responsible parties by providing a set of predefined options for common entries. By standardizing the set of available responses, they also promote the use of consistent terminology across entries and can improve the ability of users to search the data bank and compare entries easily across clinical trials.

We further note that to reduce the burden on responsible parties related to the submission of information to the data bank, *ClinicalTrials.gov* accommodates both interactive, online entry of information for a specific clinical trial and automated uploading of information that is prepared in XML format. Responsible parties submitting information on multiple clinical trials may upload information that is prepared as a batch submission. *ClinicalTrials.gov* also supports uploading of adverse event information using a spreadsheet program, such as Microsoft Excel®, so long as it conforms to the specified data format of the PRS. Additional information about submitting information to *ClinicalTrials.gov* is available at *https://prsinfo.clinicaltrials.gov.*

As described in the NPRM, the Agency might periodically make minor changes to the specific format in which responsible parties submit individual data elements and subelements to *ClinicalTrials.gov* (79 FR 69598). Such changes would not require a responsible party to submit different or more clinical trial information than is specified in the final rule, but would alter the way in which the information is entered, with the general aim of making sure the menu options contain the most relevant, useful, and convenient options for responsible parties and users of the system. For example, if the research community develops a new type of clinical trial design, we might expand the list of menu options under the Interventional Study Model subelement of the Study Design data element to include it. If we find that many of the free-text entries for the Why Study Stopped data element fall into a small number of categories, we might offer them as menu options (in addition to accepting free-text for ''Other'' reasons) to reduce the burden of data entry and improve the consistency and comparability of responses across registered clinical trials. We will provide prior notice and seek public comment on any proposed changes of substantive nature to the format of submitting clinical trial information. There may be times when changes of a technical nature may be required (*e.g.,* updates to the XML, redesign of the user interface, modifications to PRS on-screen instructions), for which no public comments will be sought.

5. 11.10—What definitions apply to this part?

Section 11.10 of the NPRM defined certain terms and data elements used in the proposed part. The terms defined in proposed § 11.10(a) included terms explicitly defined in section 402(j) of the PHS Act (*e.g.,* ''applicable clinical trial,'' ''responsible party''); terms used but not defined in section 402(j) of the PHS Act (*e.g.,* ''clinical trial''); and terms not specifically found in section 402(j) of the PHS Act but which are important for implementing the statutory provisions. With respect to terms not defined in the statute, we proposed definitions to fit within the proposed framework for the expanded data bank and for the purposes of satisfying the statutory goals, clarifying the application and operation of this proposed rule, in particular as related to information to be submitted to *ClinicalTrials.gov,* and/or for convenience. We also referenced some terms defined under the PHS Act and the FD&C Act and implementing regulations, as necessary.

For each term defined in proposed § 11.10(a), we describe below the proposed definition, any specific public comment(s) we received and our response(s), and the term and definition that is adopted in § 11.10(a) of the final rule. The list below is alphabetized according to the name assigned to the term in the final rule. For example, the term ''FDA-regulated device'' proposed in the NPRM is ''U.S. FDA-regulated device'' in the final rule, so it appears toward the end of the list.

Adverse Event

In the NPRM, we defined ''adverse event'' in § 11.10(a) as ''any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to subject's participation in the research.''

As we explained in the NPRM, ''adverse event'' is a term used but not defined in section 402(j)(3)(I) of the PHS Act to describe a certain category of clinical trial results information (79 FR 69598). Section 402(j)(3)(I)(iii) of the PHS Act requires the reporting of both anticipated and unanticipated adverse events. Current FDA regulations define the term ''adverse event'' with respect to drugs, but not to devices. (FDA regulations for devices include a different but related term, ''suspected adverse device effect,'' that is discussed in the definition of the term ''serious adverse event.'') FDA regulations for IND safety reporting requirements that were issued on September 29, 2010 (75 FR 59935), and took effect on March 28, 2011 define an adverse event as ''any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related'' (21 CFR 312.32(a)). In addition to defining the term ''adverse event,'' those FDA regulations have the additional purpose of identifying circumstances in which certain adverse events (such as those that are serious and unexpected and that also meet the definition of a ''suspected adverse reaction,'' meaning that the adverse event must have a reasonable possibility of being caused by the drug) must be reported in an expedited fashion while the trial is ongoing.

The HHS Office for Human Research Protections (OHRP) has a definition of adverse event that covers drug, device, and other interventions and includes both anticipated and unanticipated

event(s) regardless of whether they are attributed to the intervention(s) studied in the clinical trial. As discussed in OHRP's ''Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events'' (January 2007), an adverse event means ''[a]ny untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research'' [Ref. 80]. The OHRP definition was adapted from the definition used by the International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human Use (ICH) Guideline E6, Good Clinical Practice: Consolidated Guidance [Ref. 81] which was published by FDA as a guidance document in the FR in 1997 (62 FR 25692). The definition, therefore, is consistent with international norms. Although the ICH Guidelines are intended to apply to pharmaceutical products, the OHRP definition is intended to apply broadly to research in humans that involves any type of intervention.

We received comments on the adverse event definition. The commenters asserted that the definition was inconsistent with FDA's adverse event definition. One commenter noted that the definition of ''adverse event'' was vague and requested that the rule define the term to be consistent with IRB reporting requirements at continuing review. We disagree. The IRB requirements cited by the commenter are described in the OHRP guidance from which we derived the adverse event definition; this helps ensure consistency in the submission of adverse event information for applicable device clinical trials and applicable drug clinical trials. As explained above, this definition is consistent with, but not identical to, FDA's definition of ''adverse event'' for IND safety reporting in 21 CFR 312.32(a). The definition in § 11.10(a) includes not only those adverse events defined in 21 CFR 312.32 (which apply to clinical trials of drug products), but also adverse events more broadly from research participation subject to this part (*i.e.,* including clinical trials of device products) and ensures consistency with the international standard. For example, a ''suspected adverse event,'' defined by FDA as a subcategory of ''adverse event'' that requires a reasonable possibility of being caused by the drug, is also included under the definition of ''adverse event'' in § 11.10(a).

After considering these comments, we maintain the definition of ''adverse event'' in § 11.10(a) of the final rule to mean ''any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to subject's participation in the research.''

Additionally, this final rule includes a requirement to submit to *ClinicalTrials.gov* summary information about anticipated and unanticipated adverse events observed during a clinical trial (as well as a requirement to submit information about serious adverse events), regardless of attribution (*i.e.,* whether or not the investigator believes they are related to the intervention(s)). These requirements are consistent with the definition of ''adverse event'' in the final rule, which is not limited to adverse events that are anticipated, are likely to have been caused by the drug product (including biological product) or device product (or other type of intervention used in the clinical trial), or have a reasonable possibility of being related to the intervention under study. The definition of ''adverse event,'' which includes all adverse events regardless of possible attribution and regardless of whether they were anticipated, advances the statutory goal of providing more information that may be related to medical products' potential risks.

Applicable Clinical Trial

In the NPRM, we defined ''applicable clinical trial'' in § 11.10(a) to mean ''an applicable device clinical trial or an applicable drug clinical trial.'' As we explained, this definition, which is identical to the statutory definition in section 402(j)(1)(A)(i) of the PHS Act, designates the scope of clinical trials that may be subject to the requirements to submit clinical trial registration and results information as specified in this part (79 FR 69599). However, not all trials meeting the definition of an ''applicable clinical trial'' are subject to the clinical trial registration and results information submission requirements. For example, an applicable clinical trial that reached its primary completion date on or before September 27, 2007 (*i.e.,* the date of enactment of FDAAA) is not subject to section 402(j) of the PHS Act, nor is an applicable clinical trial that was ongoing as of September 27, 2007, and reached its primary completion date prior to December 26, 2007. In addition, in proposed § 11.22(b), we described an approach for determining whether a clinical study or trial meets the definition of an ''applicable clinical trial.''

We received comments on this definition. One commenter supported the proposed definition. Other commenters requested that the definition include all clinical trials, and one of these commenters further requested that the definition be amended in the final rule to include any human experiment introducing any form of a drug, device, biologic, radiation, or any other form of treatment into the human body. The definition of ''applicable clinical trial'' is set forth in section 402(j) of the PHS Act.

Based on further review and analysis, we have reconsidered whether any expanded access use falls within the definition of ''applicable clinical trial.'' For the following reasons, we have determined that no expanded access use would be considered an ''applicable clinical trial'' under section 402(j) of the PHS Act.

FDAMA (Pub. L. 105–115) contained two related provisions addressing expanded access use. FDAMA added section 561 to the FD&C Act, which specifically authorized the Secretary to permit investigational drugs and investigational devices to be made available for the diagnosis, monitoring, or treatment of serious or life-threatening diseases or conditions under certain circumstances. These so-called ''expanded access'' provisions were implemented by FDA through its IND and IDE regulations (see 21 CFR 312.300–320 and 21 CFR 812.36).

FDAMA also amended section 402 of the PHS Act to require the Secretary to establish a data bank of information on experimental drugs for serious or life-threatening diseases and conditions. This FDAMA-created data bank included two specified aspects: ''(A) A registry of clinical trials (whether federally or privately funded) of experimental treatments for serious or life-threatening diseases and conditions under regulations promulgated pursuant to section 505(i) of the [FD&C Act] . . .'' and ''(B) Information pertaining to experimental treatments for serious or life-threatening diseases and conditions that may be available—(i) under a treatment investigational new drug application that has been submitted . . . under section 561(c) of the [FD&C Act] . . .'' (currently section 402(i)(3) of the PHS Act). In addition, the FDAMA data bank could include information on ''the results of clinical trials . . . with the

consent of the sponsor . . .'' (currently section 402(i)(3) of the PHS Act).

These FDAMA provisions were implemented by NIH through the creation of *ClinicalTrials.gov*. The FDAMA provisions were subsequently amended to require information on clinical trials to also include a description of whether, and through what procedure, the manufacturer or sponsor would make the drug available for expanded access use, particularly in children (section 15(c)(2) of Public Law 107–109; 115 Stat. 1420 (2002)). Thus, there is a distinction reflected in section 402(i) of the PHS Act between a clinical trial and expanded access use.

The FDAAA provision adding current section 402(j) of the PHS Act was intended to expand the *ClinicalTrials.gov* data bank. The structure and language of section 402(j) reflect congressional intent to maintain in the data bank the same distinction between clinical trials and expanded access use. This congressional intent is evident in section 402(j)(2)(A)(ii)(II)(gg) of the PHS Act, which states that ''in the case of an applicable drug clinical trial, if the drug is not approved . . . specify whether or not there is expanded access to the drug under section 561 of the [FD&C Act] . . .'' This provision implies that expanded access use would not itself be considered an ''applicable clinical trial.''

For these reasons, we have concluded that expanded access use under section 561 of the FD&C Act does not fall within the definition of ''applicable clinical trial'' under section 402(j) of the PHS Act. However, information on the availability of investigational drug products (including biological drug products) for expanded access will continue to be required to be submitted to the *Clinical Trials.gov* database under authority of the section 402(j) registration requirements.

In the final rule, the definition of ''applicable clinical trial'' in § 11.10(a) is revised by the addition, at the end of the definition, of the following statement: ''Expanded access use under section 561 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bbb) is not an applicable clinical trial.'' Other than this change, we maintain the proposed definition of ''applicable clinical trial'' as the first sentence of the definition in the final rule: ''Applicable clinical trial means an applicable device clinical trial or an applicable drug clinical trial.'' This first sentence of the definition is identical to the statutory definition.

We also received comments specifically on the ''applicable device clinical trial'' or ''applicable drug clinical trial'' components of the proposed applicable clinical trial definition. These are addressed within the definition for each.

Applicable Device Clinical Trial

In the NPRM, we defined ''applicable device clinical trial'' in § 11.10(a) to mean (1) a prospective clinical study of health outcomes comparing an intervention with a device subject to section 510(k), 515, or 520(m) of the FD&C Act against a control in human subjects (other than a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes); and (2) a pediatric postmarket surveillance as required under section 522 of the FD&C Act.

As we explained in the NPRM, ''applicable device clinical trial'' is the term used in section 402(j)(1)(A) of the PHS Act to designate the clinical trial of a device and FDA-ordered pediatric postmarket surveillance of a device for which clinical trial information must be submitted to *ClinicalTrials.gov* under section 402(j) of the PHS Act (79 FR 69599). The proposed rule adopted, in § 11.10, the definition of applicable device clinical trial, as provided in section 402(j)(1)(A)(ii) of the PHS Act: ''(I) a prospective clinical study of health outcomes comparing an intervention with a device subject to section 510(k), 515, or 520(m) of the [FD&C] Act against a control in human subjects (other than a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes); and (II) a pediatric postmarket surveillance as required under section 522 of the [FD&C] Act.'' In addition, the proposed rule in § 11.10 adopted the definition of ''device'' in section 402(j)(1)(A)(vi) of the PHS Act as ''a device as defined in section 201(h) of the [FD&C] Act.'' We provided additional elaboration of the interpretation of applicable device clinical trial in the NPRM.

We received several comments on this definition. One commenter supported the proposed rule's applicable clinical trial definition with respect to devices, particularly that only a ''prospective'' clinical study should be considered an ''interventional study,'' and thus an applicable clinical trial. Many commenters requested that the applicable device clinical trial definition be expanded to include any trials in which a device is introduced into the human body, but they agreed that the definition should not include observational studies. One commenter requested that the definition include small device feasibility studies, which are explicitly excluded by the statutory definition. Two other commenters requested that the definition include all studies conducted under an IDE.

We have not modified the definition of ''applicable device clinical trial'' in the final rule based on these comments. The statutory definition explicitly states which trials fall within the definition of an applicable clinical trial; it does not include all device clinical trials. Section 402(j)(1)(A)(ii) of the PHS Act requires that the device must be subject to section 510(k), 515, or 520(m) of the FD&C Act. Section 402(j)(1)(A)(ii) of the PHS Act also explicitly excludes certain device feasibility studies from the ''applicable device clinical trial'' definition. A device is considered to be subject to section 510(k), 515, or 520(m) of the FD&C Act if any of the following is required before it may be legally marketed in the United States: (1) A finding of substantial equivalence under section 510(k) of the FD&C Act permitting the device to be marketed, (2) an order under section 515 of the FD&C Act approving a pre-market approval application for the device, or (3) a humanitarian device exemption (HDE) under section 520(m) of the FD&C Act. Such devices that are considered to be subject to section 510(k), 515, or 520(m) of the FD&C Act include significant risk devices for which approval of IDE is required under section 520(g) of the FD&C Act, non-significant risk devices that are considered to have an approved IDE in accordance with 21 CFR 812.2(b), or devices that are exempt from the submission requirements of 21 CFR 812 (79 FR 69600).

Some commenters also requested clarification of definitional elements. One commenter requested that the rule clarify the term ''health-outcomes'' for making an applicable clinical trial determination. We have not provided a definition of ''health outcomes'' in the final rule for the applicable device clinical trial definition. However, in the NPRM, we explained that a ''prospective clinical study of health outcomes'' is a clinical study in which the primary objective is to evaluate a defined clinical outcome related to human health (79 FR 69599). For example, a clinical study of a diagnostic device (such as an in vitro diagnostic (IVD)) in which the primary purpose is to evaluate the ability of the device to make a diagnosis of a disease or condition is related directly to human health and, therefore, would be considered a clinical study ''of health outcomes'' for purposes of this rule. We

will consider additional guidance on this term if our experience reflects it is needed.

Another commenter suggested that the term ''feasibility,'' as used in the parenthetical exclusion in the definition of ''applicable device clinical trial,'' was described in the NPRM in a way that is more limited than FDA guidance and requested clarification in the final rule. The ''feasibility study'' exclusion in the definition directly incorporates the language from section 402(j)(1)(A)(ii)(I) of the PHS Act: ''a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes'' is not an ''applicable device clinical trial.'' We explained in the NPRM that clinical studies designed primarily to determine the feasibility of a device or to test a prototype device are considered by the Agency to be clinical studies conducted to confirm the design and operating specifications of a device before beginning a full clinical trial (79 FR 69601). Feasibility studies are sometimes referred to as phase 1 studies, pilot studies, prototype studies, or introductory trials (although we note that the use of these terms does not necessarily mean that the study is a feasibility study under the definition). Our explanation of this exemption is consistent with FDA's regulation of devices. FDA published the guidance *Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies* (October 2013) to address the development and review of IDE applications for early feasibility studies of significant risk devices [Ref. 82]. For the purposes of the guidance, the guidance defines an ''early feasibility study'' as a limited clinical investigation of a device early in development, typically before the device design has been finalized, for a specific indication. The guidance further defines a ''traditional feasibility study'' as a clinical investigation that is commonly used to capture preliminary safety and effectiveness information on a near-final or final device design to adequately plan an appropriate pivotal study. Section 402(j)(1)(A)(ii)(I) of the PHS Act excludes ''small clinical trial[s] to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes'' from the definition of ''applicable device clinical trial.'' The excluded clinical trials described in this statutory definition appear to be consistent with the early feasibility study definition in the guidance, but not with that of the traditional feasibility study, which evaluates preliminary safety and effectiveness information (*i.e.,* for ''health outcomes''). Therefore, it is likely that only early feasibility studies would fall within this exclusion under the § 11.10 definition of an ''applicable device clinical trial.''

Two commenters requested that the rule define ''small,'' which is used in the definition's ''feasibility study'' exemption. One of the commenters requested that the rule use a ''threshold'' number of subjects indicated for the Enrollment data element based on an empirical database review, such as not more than 20–30 subjects for a study. The other commenter requested clarification of the term ''small'' and suggested that a device trial with at least 10 subjects could not qualify as ''small'' for the ''feasibility study'' exemption. We are not including a threshold number in the definition, because some studies with an enrolled subject total exceeding a specified threshold might be more appropriately considered a ''small feasibility study,'' while other studies with an enrolled subject total below the specified threshold, depending on the prevalence of the disease or condition, might not be considered ''small'' for the purposes of this exemption. We note that a trial with at least 10 subjects would generally not be considered ''small.''

To determine whether a device trial is an applicable device clinical device, one comment requested clarification as to whether a device that is solely packaged and/or labeled in the United States would be considered ''manufactured in'' the United States. The commenter opposed considering devices that are solely packaged and/or labeled in the United States as ''manufacture[d] in the U.S.'' and requested clarification in the final rule. Pursuant to section 510 of the FD&C Act, FDA's jurisdiction extends to the ''manufacture, preparation, propagation, compounding or processing'' of devices, which term is defined to include ''repackaging or otherwise changing the container, wrapper, or labeling or any . . . device package in furtherance of the distribution of the . . . device from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer or user.'' The NPRM used the term ''manufacture'' as a short-hand for all device activities within FDA's jurisdiction. Therefore, a device product that is packaged and/or labeled in the United States would be considered ''manufactured'' in the United States and subject to section 510(k), 515, or 520(m) of the FD&C Act.

After considering the comments, we maintain the definition of ''applicable device clinical trial'' in § 11.10(a), except that we have clarified the status of certain clinical trials of combination products, made clear that the term ''device'' refers to a particular manufacturer's device product, and included the applicable United States Code (U.S.C.) statutory citations. In § 11.10(a) of the final rule, we define ''applicable device clinical trial'' to mean ''(1) [a] prospective clinical study of health outcomes comparing an intervention with a device product subject to section 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360(k), 21 U.S.C. 360e, 21 U.S.C. 360j(m)) against a control in human subjects (other than a small clinical trial to determine the feasibility of a device product, or a clinical trial to test prototype device products where the primary outcome measure relates to feasibility and not to health outcomes); (2) [a] pediatric postmarket surveillance of a device product as required under section 522 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 3601); or (3) [a] clinical trial of a combination product with a device primary mode of action under 21 CFR part 3, provided that it meets all other criteria of the definition under this part.''

The first part of the definition in section 402(j)(1)(A)(ii)(I) of the PHS Act defines a clinical study as an applicable device clinical trial if it meets the following four criteria: (1) It is a prospective clinical study of health outcomes; (2) it compares an intervention with a device against a control in human subjects; (3) the studied device is subject to section 510(k), 515, or 520(m) of the FD&C Act; and (4) it is other than a small clinical trial to determine the feasibility of a device or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes. Except as described below with regard to pediatric postmarket surveillances of a device product, if a clinical investigation fails to meet one or more of these criteria, it would not be considered an applicable device clinical trial. We have considered the meaning of these criteria carefully and our interpretation follows.

(1) ''Prospective clinical study of health outcomes.'' First, we interpret the term ''clinical study,'' with respect to a device product. We interpret ''clinical study'' with respect to a device product to mean an investigation in which a device product is used in one or more human subjects. For the purposes of

interpreting the term ''clinical study,'' we consider the term ''human subject'' to have the same meaning as the term ''subject,'' which is defined in FDA regulations as a ''human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A subject may be in normal health or may have a medical condition or disease'' (see 21 CFR 812.3(p)). For the purposes of only the requirements under section 402(j) of the PHS Act and this rule, the term ''human subject'' does not include de-identified human specimens [Ref. 83]. Note that we use the term ''participant'' interchangeably with ''human subject'' in this document.

The term ''study'' is often used interchangeably with the term ''investigation.'' As pertaining to device products, ''investigation'' is defined as ''a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device.'' (See 21 CFR 812.3(h).) Although FDA regulations pertaining to device products do not specifically define the term ''clinical investigation,'' that term is defined in FDA regulations pertaining to clinical investigations of drug products (including biological products) as ''any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects,'' where ''experiment'' is defined as ''any use of a drug except for the use of a marketed drug in the course of medical practice'' (see 21 CFR 312.3). In our view, these definitions can be applied to trials of a device product by defining a ''clinical study of a device product'' as ''any experiment in which a device product is administered, dispensed to, or used involving, one or more human subjects,'' defining an ''experiment'' as ''any use of a device product except for the use of a marketed device product in the course of medical practice,'' and using the definition of ''subject'' described above (from 21 CFR 812.3(p)). This interpretation helps improve consistency between definitions of the terms ''applicable device clinical trial'' and ''applicable drug clinical trial.'' In addition, our proposed interpretation of a ''clinical study'' of a device product would include studies in which subjects are assigned to specific interventions according to a study protocol. Studies in which a device product is used on a patient as part of routine medical care and not because of a study or protocol would not be considered clinical studies for the purposes of this rule. An example of studies that would not be considered clinical investigations include situations in which, after a device product has been administered to patients in the course of routine medical practice by a healthcare provider, a researcher not associated with the administration of the device product reviews the patients' records in order to assess certain effects, interviews the patients to assess certain impacts, or collects longitudinal data to assess health outcomes.

Second, turning to our interpretation of the term ''prospective,'' we consider a prospective clinical study to be any study that is not retrospective or, in other words, one in which subjects are followed forward in time from a well-defined point (*i.e.,* the baseline of the study) or are assessed at the time the study intervention is provided. A prospective clinical study may also have non-concurrent (*e.g.,* historical) control groups. An example of a retrospective study, and therefore not an applicable device clinical trial, is a study in which subjects are selected based on the presence or absence of a particular event or outcome of interest (*e.g.,* from hospital records or other data sources) and their past exposure to a device product is then studied.

Third, with respect to our interpretation of the phrase ''of health outcomes,'' for the purposes of the definition of ''applicable device clinical trial,'' we consider a ''prospective clinical study of health outcomes'' to be a clinical study in which one or more of the primary or secondary outcome measures are biomedical or health-related. For example, a clinical study of a diagnostic device (such as an IVD) in which the primary outcome measure is the number of subjects with the correct diagnosis, would be considered a clinical study of health outcomes for the purposes of this proposed rule.

(2) ''Comparing an intervention with a device against a control in human subjects.'' We interpret the phrase an ''intervention with a device'' to be an intervention in which a device product is used on a human subject in the course of a study. As stated above, the meaning of the term ''human subject'' is consistent with the definition of ''subject'' in 21 CFR 812.3(p), except that for the purposes of only the requirements under this part, the term ''human subject'' does not include de-identified human specimens. We interpret the term ''intervention'' broadly, to include various techniques for using the device product such as, among others, device regimens and procedures and the use of prophylactic, diagnostic, or therapeutic agents.

A clinical study is considered, or intended, to ''compare an intervention with a device against a control in human subjects'' when it compares differences in the biomedical or health-related outcomes between human subjects who received an intervention that included a device product and human subjects who received other interventions or no intervention (*e.g.,* comparison with another device product, comparison with usual clinical care that did not involve a device product). The intervention under study may be one with a device product that has never been cleared or approved or one with a device product that has been cleared or approved, regardless of whether the clearance or approval is for the use being studied. Such controlled clinical studies include not only concurrent control groups, but also non-concurrent controls such as historical controls (*e.g.,* literature, patient records, human subjects as their own control) or outcomes using objective performance criteria such as performance criteria based on broad sets of data from historical databases (*e.g.,* literature or registries) that are generally recognized as acceptable values. As discussed further in the definition of ''control or controlled,'' we clarify for the purposes of this part that all interventional studies, whether single or multi-arm, with a pre-specified outcome are considered to be controlled (*i.e.,* comparing an intervention against a control).

As discussed above, expanded access protocols under section 561 of the FD&C Act, under which investigational devices are made available under certain circumstances, do not fall within the definition of ''applicable device clinical trial.''

(3) ''A device subject to section 510(k), 515, or 520(m)'' of the FD&C Act. A device product is considered to be subject to section 510(k), 515, or 520(m) of the FD&C Act if any of the following is required before it may be legally marketed in the United States: (1) A finding of substantial equivalence under section 510(k) permitting the device product to be marketed, (2) an order under section 515 of the FD&C Act approving a pre-market approval application for the device product, or (3) an HDE under section 520(m) of the FD&C Act. Device products that are considered to be subject to section 510(k), 515, or 520(m) of the FD&C Act include significant risk devices for which approval of an IDE is required under section 520(g) of the FD&C Act, non-significant risk devices that are considered to have an approved IDE in accordance with 21 CFR 812.2(b), or

device products that are exempt from the submission requirements of 21 CFR part 812.

If a clinical study of a device product includes sites both within the United States (including any U.S. territory) and outside of the United States, and if any of those sites is using (for the purposes of the clinical study) a device product that is subject to section 510(k), 515, or 520(m) of the FD&C Act, we would consider the entire clinical study to be an applicable device clinical trial, provided that it meets all of the other criteria of the definition under this part. However, a clinical study of a device product that is being conducted entirely outside of the United States (*i.e.,* does not have any sites in the United States or in any U.S. territory) and is not conducted under an IDE may not be a clinical study of a device product subject to section 510(k), 515, or 520(m) of the FD&C Act and, therefore, is not an applicable device clinical trial, depending on where the device product being used in the clinical study is manufactured. If the device product is manufactured in the United States or any U.S. territory, and is exported for study in another country (whether it is exported under section 801(e) or section 802 of the FD&C Act), the device product is considered to be subject to section 510(k), 515, or 520(m) of the FD&C Act. If the device product is manufactured outside of the United States or its territories, and the clinical study sites are all outside of the United States and/or its territories, the device product would not be considered to be subject to section 510(k), 515, or 520(m) of the FD&C Act. A device product that is packaged and/or labeled in the United States would be considered ''manufactured'' in the United States subject to section 510(k), 515, or 520(m) of the FD&C Act.

(4) ''Other than a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes.'' Clinical studies designed primarily to determine the feasibility of a device product or to test a prototype device are considered by the Agency to be clinical studies conducted to confirm the design and operating specifications of a device product before beginning a full clinical trial. Feasibility studies are not considered applicable device clinical trials under this part.

The second part of the definition in section 402(j)(1)(A)(ii)(II) of the PHS Act specifies that an applicable device clinical trial includes ''pediatric postmarket surveillance as required under section 522 of the Federal Food, Drug, and Cosmetic Act.'' Postmarket surveillances can take many forms, from literature reviews to controlled clinical trials. Based on the statutory language, any pediatric postmarket surveillance of a device product under section 522 of the FD&C Act, regardless of its design, is an applicable device clinical trial.

In addition, a combination product may include a device subject to section 510(k), 515, or 520(m) of the FD&C Act, as well as a drug (including a biological product) subject to section 505 of the FD&C Act or section 351 of the PHS Act (see 21 CFR 3.2(e)). Drugs (including biological products) and devices do not lose their discrete regulatory identities when they become constituent parts of a combination product. In general, the regulatory requirements specific to each constituent part of a combination product also apply to the combination product itself. However, because some requirements of section 402(j) of the PHS Act are different for applicable device clinical trials than for applicable drug clinical trials, there is a need for clarity as to which requirements apply to applicable clinical trials of combination products that include device and drug constituent parts. In order to provide this clarity, the final rule specifies that an applicable clinical trial of a combination product with a device primary mode of action under 21 CFR part 3 would be considered an applicable device clinical trial, provided that it meets all other criteria of the definition under § 11.10(a), and likewise, a clinical trial of a combination product with a drug primary mode of action under 21 CFR part 3 would be considered an applicable drug clinical trial, provided that it meets all other criteria of the definition under § 11.10(a).

Applicable Drug Clinical Trial

In the NPRM, we defined ''applicable drug clinical trial'' in § 11.10(a) to mean ''a controlled clinical investigation, other than a phase 1 clinical investigation, of a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to section 351 of the Public Health Service Act, where 'clinical investigation' has the meaning given in 21 CFR 312.3 (or any successor regulation) and 'phase 1' has the meaning given in 21 CFR 312.21 (or any successor regulation).''

As we explained in the NPRM, ''applicable drug clinical trial'' is the term used in section 402(j)(1)(A) of the PHS Act to designate a clinical trial involving a drug (including a biological product) for which clinical trial information must be submitted to *ClinicalTrials.gov* under section 402(j) of the PHS Act (79 FR 69601). The proposed rule in § 11.10 adopted the definition of applicable drug clinical trial in section 402(j)(1)(A)(iii)(I) of the PHS Act and further clarified that, as specified in sections 402(j)(1)(A)(iii)(II) and (III), the term ''clinical investigation'' has the meaning given in 21 CFR 312.3 (or any successor regulation) and ''phase I'' has the meaning given in 21 CFR 312.21 (or any successor regulation). We did, however, propose to replace ''phase I'' with ''phase 1,'' to be consistent with the numbering scheme used in FDA regulations (21 CFR 312.21). We provided additional elaboration of the interpretation of the term ''applicable drug clinical trial'' in the NPRM (79 FR 69601).

In addition, for the purposes of implementing the rule, we proposed to treat certain clinical trials of combination products as applicable drug clinical trials. Combination products are defined in 21 CFR 3.2(e). A combination product is comprised of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, a biological product, and a device that, for example, are physically, chemically, or otherwise combined or mixed and produced as a single entity or are separate products packaged together in a single package or as a unit (see 21 CFR 3.2(e)(1) and (2)). Because the definition of a ''drug'' in proposed § 11.10 included a biological product, we stated in the proposed rule that a combination product would always consist, in part, of a drug. Therefore, we proposed to treat clinical trials of combination products that meet the definition in 21 CFR 3.2(e) as applicable drug clinical trials, for the purposes of the rule, as long as the clinical trial of the combination product is a controlled clinical investigation, other than a phase 1 clinical investigation, and the combination product is subject to sections 505 of the FD&C Act and/or section 351 of the PHS Act and/or section 510(k), 515, or 520(m) of the FD&C Act.

Several commenters addressed the proposed definition. Many commenters requested that the definition of ''applicable drug clinical trial'' include ''phase 0'' or phase 1 studies. One commenter requested that the definition include all interventional drug clinical trials, including phases 1–4, consistent with the EU Clinical Trial Registration requirements. Several commenters requested that the applicable drug clinical trial definition be expanded to include any trials in which a drug is introduced into the human body, but they agreed that the definition should

not include observational studies. One commenter, as noted in the discussion of an applicable device clinical trial, opposed considering packaging or labeling in the United States as ''manufacture[d] in the U.S.'' and requested clarification in the final rule. Another commenter requested that the rule clarify whether foreign trials not conducted under an IND with a drug product not exported from the United States, but which are subsequently included as a pivotal trial in a new drug application (NDA) or biologics license application (BLA), should be considered applicable clinical trials and therefore listed in Item 10 of Form FDA 3674.

Section 402(j)(1)(A)(iii)(I) of the PHS Act explicitly requires that the drug must be subject to section 505 of the FD&C Act or section 351 of the PHS Act and explicitly exempts phase 1 studies from the definition of ''applicable drug clinical trial'' and, therefore, from the registration and results information submission requirements. With respect to the comment regarding packaging or labeling, pursuant to section 510 of the FD&C Act, FDA's jurisdiction extends to the ''manufacture, preparation, propagation, compounding or processing'' of drugs, which term is defined to include ''repackaging or otherwise changing the container, wrapper, or labeling or any drug package . . . in furtherance of the distribution of the drug . . . from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer or user.'' The NPRM used the term ''manufacture'' as short-hand for all drug activities within FDA's jurisdiction. Therefore, a drug product that is packaged and/or labeled in the United States would be considered ''manufactured'' in the United States subject to section 505 of the FD&C Act or section 351 of the PHS Act. With respect to the question about a foreign trial, the issue of which trials should be listed on Form FDA 3674 is outside the scope of this rulemaking.

Commenters requested that we change the interpretation of the terms ''applicable drug clinical trial'' and ''applicable device clinical trial'' for combination products. The commenters asked that we rely on the ''primary mode of action'' (see 21 CFR 3.2(m)) to determine whether a combination product is an applicable drug clinical trial or applicable device clinical trial. We agree with these commenters and have modified the regulations to incorporate this change. FDA regulations in 21 CFR part 3 specify that the primary mode of action of a combination product is the single mode of action that provides the most important therapeutic action of the intended therapeutic effects of the combination product. A combination product with a device primary mode of action under 21 CFR part 3 would be considered an applicable device clinical trial, provided that it meets all other criteria of the definition under this part. A combination product with a drug primary mode of action under 21 CFR part 3 would be considered an applicable drug clinical trial, provided that it meets all other criteria of the definition under this part.

In § 11.10(a) of the final rule, we define ''applicable drug clinical trial'' to mean a controlled clinical investigation, other than a phase 1 clinical investigation, of a drug product subject to section 505 of the FD&C Act (21 U.S.C. 355) or a biological product subject to section 351 of the PHS Act (42 U.S.C. 262), where ''clinical investigation'' has the meaning given in 21 CFR 312.3 and ''phase 1'' has the meaning given in 21 CFR 312.21. In addition, a clinical trial of a combination product, where the combination product meets the definition in 21 CFR 3.2(e) and has a drug primary mode of action under 21 CFR part 3 will be considered an applicable drug clinical trial, as long as the clinical trial of the combination product is a controlled clinical investigation, other than a phase 1 clinical investigation, and the combination product is subject to section 505 of the FD&C Act and/or section 351 of the PHS Act.

We interpret the definition of applicable drug clinical trial under section 402(j)(1)(A)(iii) of the PHS Act as having four operative elements: (1) ''Controlled''; (2) ''clinical investigation''; (3) ''other than a phase [1] clinical investigation''; and (4) ''drug product subject to section 505 of the Federal Food, Drug, and Cosmetic Act or section 351 of th[e] [Public Health Service] Act.'' A clinical investigation that meets all four elements is considered an applicable drug clinical trial. Conversely, a clinical investigation that does not meet one or more of these criteria would not be considered an applicable drug clinical trial. We have carefully considered these four criteria, and our interpretation follows in an order that facilitates the explanation.

(1) With regard to a ''drug product subject to section 505 of the Federal Food, Drug, and Cosmetic Act or section 351 of th[e] [Public Health Service] Act,'' § 11.10(a) adopts the definition of the term ''drug'' in section 402(j)(1)(A)(vii) of the PHS Act as follows: ''a drug as defined in section 201(g) of the [FD&C Act] or a biological product as defined in section 351 of th[e] [PHS Act].'' Section 11.10(a) also clarifies in the definition of ''applicable drug clinical trial'' that the term ''drug'' refers to a particular manufacturer's drug product. In keeping with the requirements of the FD&C Act and section 351 of the PHS Act, a drug product or a biological product is considered to be ''subject to section 505 of the [FD&C Act] or section 351 of th[e] [PHS Act],'' as applicable, if it is the subject of an approved NDA or licensed BLA or if an approved NDA or licensed BLA would be required in order for that drug product or biological product to be legally marketed. A non-prescription drug product that is or could be marketed under an existing over-the-counter drug monograph (see 21 CFR 330–358) is not considered ''subject to section 505 of the [FD&C Act].''

As discussed above, a clinical trial of a combination product with a drug primary mode of action under 21 CFR part 3 would be considered an applicable drug clinical trial, provided that it meets all other criteria of the definition under § 11.10(a).

A drug product or a biological product that is subject to section 505 of the FD&C Act or section 351 of the PHS Act and, therefore, would require an approved NDA or licensed BLA in order to be marketed legally can be shipped for the purpose of conducting a clinical investigation of that product if an IND is in effect. Drug products (including biological products) that are being studied under an IND are considered ''subject to section 505 of the FD&C Act'' both because (in most situations) the drug product being studied would need an approved NDA or licensed BLA to be marketed legally, and because INDs are issued by FDA pursuant to the authority in section 505(i) of the FD&C Act. We note that a substance characterized by a responsible party as a dietary supplement could be considered a ''drug'' subject to section 505 of the FD&C Act under the applicable drug clinical trial definition if the trial is studying a use that meets the drug definition under the FD&C Act. Furthermore, whether a drug product or biological product is subject to section 505 of the FD&C Act or section 351 of the PHS Act is a different question from whether a clinical investigator would need to obtain an IND from FDA before beginning to enroll human subjects in a clinical investigation. Therefore, a drug product or biological product being studied in a clinical investigation can be subject to section 505 of the FD&C Act or section 351 of the PHS Act, even if a clinical investigation of that drug product or biological product is ''IND

exempt'' (*i.e.,* does not require an IND because that clinical investigation falls within 21 CFR 312.2(b)). Therefore, provided it meets all other criteria of the definition, a clinical investigation of a drug product (including a biological product) can be an applicable drug clinical trial under section 402(j) of the PHS Act and this part, even if it does not require an IND. Furthermore, if a sponsor chooses to obtain an IND (issued under section 505 of the FD&C Act) for a clinical investigation of a drug product (including a biological product) that is not otherwise subject to section 505 of the FD&C Act or section 351 of the PHS Act, the sponsor, in so doing, agrees to regulation under section 505 of the FD&C Act, and that clinical investigation thus will be considered an applicable drug clinical trial, provided that it meets all other criteria of the definition under this part.

If a clinical investigation of a drug product (including a biological product) includes sites both within the United States (including any U.S. territory) and outside of the United States, and any of those sites is using (for the purposes of the clinical investigation) a drug product or biological product that is subject to section 505 of the FD&C Act or section 351 of the PHS Act, we would consider the entire clinical investigation to be an applicable drug clinical trial, provided that it meets all other criteria of the definition under this part. However, a clinical investigation of a drug product (including a biological product) that is being conducted entirely outside of the United States (*i.e.,* does not have any sites in the United States or in any U.S. territory) may not be a clinical investigation of a drug product or biological product subject to section 505 of the FD&C Act or section 351 of the PHS Act, and therefore not an applicable drug clinical trial, depending on where the drug product (including biological product) being used in the clinical investigation is manufactured. If the drug product (including a biological product) is manufactured in the United States or any U.S. territory, and is exported for study in another country under an IND (whether pursuant to 21 CFR 312.110 or section 802 of the FD&C Act), the drug product or biological product is considered to be subject to section 505 of the FD&C Act or section 351 of the PHS Act (as applicable), and the clinical investigation may be an applicable drug clinical trial, provided that it meets all other criteria of the definition under this part. If the drug product (including a biological product) is manufactured outside of the United States or its territories, the clinical investigation sites are all outside of the United States, and the clinical investigation is not being conducted under an IND, the drug product or biological product would not be considered to be subject to section 505 of the FD&C Act or section 351 of the PHS Act, and the clinical investigation would not be an applicable drug clinical trial. A drug product that is packaged and/or labeled in the United States would be considered ''manufactured'' in the United States subject to section 505 of the FD&C Act or section 351 of the PHS Act.

(2) With regard to ''clinical investigation,'' section 402(j)(1)(A)(iii)(II) of the PHS Act provides that the term ''clinical investigation'' has the meaning given to it in 21 CFR 312.3, which defines a ''[c]linical investigation'' as ''any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects.'' The regulation further defines an ''experiment'' as ''any use of a drug except for the use of a marketed drug in the course of medical practice.''

The FDA definition of a ''clinical investigation'' of a drug includes studies in which human subjects are assigned to specific interventions according to a research protocol. However, a situation in which a drug product is administered or provided to a patient as part of routine medical care and not under a study or research protocol is not considered a clinical investigation for the purposes of this rulemaking. A clinical investigation does not include situations in which, after a drug product has been administered to patients in the course of routine medical practice by a healthcare provider, a researcher not associated with the administration of the drug product reviews the patients' records to assess certain effects, interviews the patients to assess certain impacts, or collects longitudinal data to track health outcomes. Similarly, a situation in which a healthcare provider only observes and records the effects of the use of a marketed drug product in the course of his or her routine medical practice is not considered a clinical investigation under this definition. Because these activities are not considered clinical investigations under 21 CFR 312.3, they are not considered applicable drug clinical trials under section 402(j) of the PHS Act and this part. Accordingly, in the approach described in § 11.22(b)(2), we consider an interventional study (or investigation) of a drug product to be one of the criteria for determining an applicable drug clinical trial.

(3) With regard to ''controlled,'' we consider a ''controlled clinical investigation'' to be one that is designed to permit a comparison of a test intervention with a control to provide a quantitative assessment of the effect of the drug product. The purpose of the control is to distinguish the effect of a drug product from other influences, such as spontaneous change in the course of diseases, the placebo effect, or biased observation. The control will provide data on what happens to human subjects who have not received the test intervention or who have received a different intervention. Generally, the types of controls that are used in clinical investigations are as follows: (1) Placebo concurrent control, (2) dose-comparison control, (3) no intervention concurrent control, (4) active intervention concurrent control, and (5) historical control (see 21 CFR 314.126(b)). As discussed further in the definition of ''control or controlled,'' we are clarifying for the purpose of this part that all interventional studies, both single-armed and multi-armed, with a pre-specified outcome measure are considered to be controlled (*i.e.,* comparing an intervention against a control).

In our view, a clinical investigation designed to demonstrate that an investigational drug product is bioequivalent to a previously approved drug product, or to demonstrate comparative bioavailability of two products (such as for the purposes of submitting an abbreviated new drug application (ANDA) under 21 U.S.C. 355(j) or an NDA as described in 21 U.S.C. 355(b)(2)), is considered to be a controlled clinical investigation. In this case, the control generally is the previously approved drug product. However, as discussed below, a bioequivalence or comparative bioavailability study that falls within the scope of 21 CFR 320.24(b)(1), (2), or (3) shares many of the characteristics of a phase 1 study and is considered to be a phase 1 trial (and, therefore, not an applicable clinical trial) in this rule.

As discussed above, expanded access protocols under section 561 of the FD&C Act do not fall within the definition of ''applicable drug clinical trial.''

(4) With regard to the ''other than a phase [1] clinical investigation'' element, an applicable drug clinical trial is defined in section 402(j)(1)(A)(iii) of the PHS Act to exclude phase 1 clinical investigations, consistent with 21 CFR 312.21. Under 21 CFR 312.21(a)(1), a phase 1 study ''includes the initial introduction of an investigational new drug into humans. Phase 1 studies are typically closely monitored and may be

conducted in patients or normal volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, phase 2 studies. The total number of subjects and patients included in phase 1 studies varies with the drug, but is generally in the range of 20 to 80.'' Under 21 CFR 312.21(a)(2), ''[p]hase 1 studies also include studies of drug metabolism, structure-activity relationships, and mechanism of action in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes.'' Clinical trials that are phase 1 studies under 21 CFR 312.21 are not applicable drug clinical trials. Clinical trials that are identified as phase 1/phase 2 trials (*i.e.,* trials with characteristics of both phase 1 and phase 2 studies) are not considered phase 1 studies and may be applicable drug clinical trials if they meet the other specified criteria.

Under certain circumstances, a clinical investigation designed to demonstrate that an investigational drug product is bioequivalent to a previously approved drug product, or to demonstrate comparative bioavailability of two products (such as for the purposes of submitting an ANDA under 21 U.S.C. 355(j) or an NDA as described in 21 U.S.C. 355(b)(2)) will be considered to be a phase 1 clinical investigation under 21 CFR 312.21 for the purposes of determining whether a particular clinical trial is an applicable drug clinical trial under section 402(j)(1)(A)(iii) of the PHS Act. Although phase 1 clinical investigations are generally designed to fit sequentially within the development plan for a particular drug product, and to develop the data that will support beginning phase 2 clinical investigations, 21 CFR 312.21(a) does not limit phase 1 clinical investigations to that situation. A bioequivalence or comparative bioavailability study that falls within the scope of 21 CFR 320.24(b)(1), (2), or (3) shares many of the characteristics of a phase 1 clinical investigation as described in 21 CFR 312.21(a), and, therefore, is considered to be a phase 1 clinical investigation for the purposes of section 402(j) of the PHS Act (including in this rule). However, a bioequivalence or comparative bioavailability clinical trial that falls within the scope of 21 CFR 320.24(b)(4) does not share the characteristics of a phase 1 clinical trial as described in 21 CFR 312.21(a), and, therefore, is not considered to be a phase 1 clinical trial for the purposes of section 402(j) of the PHS Act (including in this rule).

Approved Drug

In the NPRM, we defined ''approved drug'' in proposed § 11.10(a) to mean ''a drug that is approved for any indication under section 505 of the Federal Food, Drug, and Cosmetic Act or a biological product licensed for any indication under section 351 of the Public Health Service Act'' (see 79 FR 69603). We received several comments on this proposed definition asserting that a clinical trial for a new use of an approved drug product would subject the clinical trial to the rule's requirements. We agree that clinical trials of new uses for an approved drug product can be subject to the rule, if the clinical trial also meets the definition of an ''applicable drug clinical trial'' and meets the requirements of § 11.22.

In the final rule, we maintain the definition except the final rule definition uses the term ''use'' instead of ''indication'' for further clarity. As explained elsewhere, for the purposes of this rule only, we interpret ''use'' to include ''indication.'' We also clarified in the final rule that ''drug'' refers to a particular manufacturer's drug product. We also include the applicable U.S.C. statutory citations in the definition. Based on our experience with *ClinicalTrials.gov* and routine queries from users, we are also clarifying two issues here. First, a drug product that is not approved for any use but is ''tentatively approved'' by FDA, as described in sections 505(j)(5)(B)(iv)(II)(dd)(AA) and (BB) of the FD&C Act, is not considered to be an approved drug for the purposes of section 402(j) of the PHS Act, and therefore is not included in the rule's definition of ''approved drug.'' Second, a drug product approved by FDA but for which approval is later withdrawn under section 505(e) of the FD&C Act, and that is no longer approved for any use, is not considered an approved drug for purposes of this part.

Approved or Cleared Device

In the NPRM, we defined ''approved or cleared device'' in § 11.10(a) to mean ''a device that is cleared for any indication under section 510(k) of the Federal Food, Drug, and Cosmetic Act or approved for any indication under sections 515 or 520(m) of that Act.'' As we explained, section 402(j)(2)(D)(ii)(II) of the PHS Act uses the phrase ''a device that was previously cleared or approved'' to refer to a subset of devices that, if studied in an applicable device clinical trial, would trigger certain requirements under this proposed part with respect to the public posting of clinical trial information (79 FR 69603). Accordingly, we proposed defining the term ''approved or cleared device'' to refer to any device that has been approved or cleared under the applicable section of the FD&C Act for any indication, even if the applicable device clinical trial studies the device for an unapproved or uncleared use. We received several comments on this definition asserting that a clinical trial for a new use of an approved or cleared device would subject the clinical trial to the rule's requirements. We agree that clinical trials of new uses for an approved or cleared device can be subject to the rule, if the clinical trial also satisfies the ''applicable device clinical trial'' definition elements and other triggering requirements, such as § 11.22 for registration.

The final rule maintains the definition, except that the final rule definition uses the term ''use'' instead of ''indication'' for further clarity. As explained elsewhere, for the purposes of this rule only, we interpret ''use'' to include ''indication.'' We also clarified that the term ''device'' refers to a particular manufacturer's device product and include the applicable U.S.C. statutory citations in the definition.

Arm

In the NPRM, we defined ''arm'' in § 11.10(a) to mean ''a pre-specified group or subgroup of human subjects in a clinical trial assigned to receive specific intervention(s) (or no intervention) according to a protocol.'' We received no comments on this definition, and we maintain the definition in the final rule, except the final rule definition modifies the phrase ''human subjects'' to ''human subject(s)'' for further clarity.

Clinical Study

The NPRM did not propose a definition of ''clinical study'' in § 11.10(a) but we are including the term and data element in this final rule. The term ''clinical study'' is used in the statutory definition of ''applicable device clinical trial'' (see section 402((j)(1)(A)(ii)(I) of the PHS Act), and the NPRM discussed ''clinical study'' in the context of this definition (79 FR 69599). ''Clinical study'' is also used in the definition of ''clinical trial'' in § 11.10(a) of this regulation. To provide

further clarity, we define the term ''clinical study'' in § 11.10(a) to mean ''research according to a protocol involving one or more human subjects to evaluate biomedical or health-related outcomes, including interventional studies and observational studies.'' This definition is consistent with our discussion of the term's meaning in the NPRM (79 FR 69599).

Clinical Trial

In the NPRM, we defined ''clinical trial'' in § 11.10(a) to mean ''a clinical investigation or a clinical study in which human subjects are prospectively assigned, according to a protocol, to one or more interventions (or no intervention) to evaluate the effects of the interventions on biomedical or health-related outcomes.'' As we explained, the definition explicitly included biomedical in addition to health-related outcomes because we have defined the term ''clinical trial'' to include phase 1 studies, which may measure physiological changes that are biomedical in nature but may not be related to health effects (79 FR 69603). We defined the term ''clinical trial'' to include phase 1 studies, in part, because phase 1 studies may be voluntarily submitted under section 402(j)(4)(A) of the PHS Act. The restriction of the scope of this definition to clinical investigations or studies in which human subjects are prospectively assigned to interventions was intended to distinguish clinical trials (interventional studies) from observational studies, in which the investigator does not assign human subjects to interventions, but, for example, observes patients who have been given interventions in the course of routine clinical care. Observational studies may also include retrospective reviews of patient medical records or relevant literature.

Several commenters addressed the proposed definition. Many commenters requested that we define ''clinical trial'' to mean any trial in which a drug, biologic, device, radioactive material, or any other foreign body is introduced into the human body. We do not use this alternative definition because it includes the use of drugs, biologics, devices, or radioactive materials provided to a patient as part of routine medical care, such as in observational studies. Other commenters requested that we resolve any differences between the proposed rule's definition and the definitions of ''clinical trial'' used by NIH and ICMJE, and the definition of ''qualified clinical trial'' used by the Centers for Medicare & Medicaid Services. These commenters expressed concern that any differences in definitions could lead to inconsistencies in how responsible parties must register and report results information across these contexts. We note that the definition of ''clinical trial'' we proposed is consistent with the NIH, ICMJE, and WHO definitions, although the scope of what needs to be registered differs from other contexts because of the requirements of section 402(j) of the PHS Act. We note that the *ClinicalTrials.gov* system allows for the reporting of studies that are not subject to (or are independent of) requirements under section 402(j) of the PHS Act, including under different timelines and with additional information, which means that reporting in these other contexts is not impeded. Finally, the proposed definition of ''clinical trial'' did not distinguish between approved, licensed, or cleared uses and unapproved, unlicensed, or uncleared uses, and therefore human testing of an approved drug or device for a new use can fall within the scope of a clinical trial. These clinical trials, though, must meet the definition of an ''applicable clinical trial'' and other conditions of the regulation in order for registration and results information reporting to be required under section 402(j) of the PHS Act.

In the final rule, we maintain the proposed definition for ''clinical trial,'' except the final rule definition modifies the phrase ''human subjects'' to ''human subject(s)'' for further clarity. In terms of defining the scope of a clinical trial, we recognize that it may sometimes be difficult to determine whether two or more closely related studies should be considered a single clinical trial for the purposes of this part. In general, a clinical trial has a defined group of human subjects who are assigned to interventions, and the collected data are assessed and analyzed, based on a protocol. However, when two different studies use the same protocol but involve different groups of human subjects, and the plan is to analyze the data from the two studies separately, the two studies should be considered separate clinical trials. This is distinct from a situation in which multiple sites of the same clinical trial follow the same protocol with different groups of human subjects, but the intention is to analyze the primary outcome measure(s) with pooled data from all the study sites. Additionally, when some (or all) human subjects from a clinical trial are offered the opportunity to participate in an additional clinical trial that was not part of the original protocol (*e.g.,* a follow-on study), and participation requires a separate consent process, the additional clinical trial would generally be considered a separate clinical trial.

Clinical Trial Information

In the NPRM, we defined ''clinical trial information'' in § 11.10(a) to mean ''the data elements, including clinical trial registration information and clinical trial results information, the responsible party is required to submit to *ClinicalTrials.gov* under this part.'' As we explained, section 402(j)(1)(A)(iv) of the PHS Act expressly provides that ''[c]linical trial information'' means ''those data elements that the responsible party is required to submit under paragraph (2) or under paragraph (3)'' of section 402(j) of the PHS Act (79 FR 69603). Paragraph (2) refers to registration requirements, including the registration information that is included in proposed § 11.28, and paragraph (3) refers to results information submission requirements, including results information in proposed § 11.48. Section 402(j)(3)(I)(v) of the PHS Act also expressly provides that adverse event information included in the data bank pursuant to paragraph (3)(I) ''is deemed to be clinical trial information included in such data bank pursuant to subparagraph (C).''

We received no comments on this definition. We are clarifying on our own initiative that clinical trial information is submitted to *ClinicalTrials.gov* as specified in section 402(j) of the PHS Act and as specified in the final regulations; we also corrected a typographical error. Therefore, for the purposes of the final rule, clinical trial information means ''the data elements, including clinical trial registration information and clinical trial results information, that the responsible party is required to submit to *ClinicalTrials.gov*, as specified in section 402(j) of the Public Health Service Act (42 U.S.C. 282(j)) and this part.''

Clinical Trial Registration Information

In the NPRM, we defined ''clinical trial registration information'' in § 11.10(a) to mean ''the data elements that the responsible party is required to submit to *ClinicalTrials.gov*, as listed under § 11.28.'' We received no comments on this definition. We clarify that the full set of data elements specified in § 11.28 must be submitted in order to register an applicable clinical trial for applicable clinical trials with an initiation date on or after the effective date of the final rule, as discussed further in section IV.F. Effective Date, Compliance Date, and Applicability of Requirements in this part. For

applicable clinical trials with an initiation date before the effective date of the final rule, clinical trial registration information must be submitted as specified in section 402(j)(2)(A)(ii) of the PHS Act. Therefore, for the purposes of the final rule, clinical trial registration information means ''the data elements that the responsible party is required to submit to *ClinicalTrials.gov,* as specified in section 402(j)(2)(A)(ii) of the Public Health Service Act (42 U.S.C. 282(j)(2)(A)(ii)) or § 11.28, as applicable.''

Clinical Trial Results Information

In the NPRM, we defined ''clinical trial results information'' in § 11.10(a) to mean ''the data elements that the responsible party is required to submit to *ClinicalTrials.gov* under § 11.48 or, if applicable, § 11.60(a)(2)(i)(B).'' We noted that clinical trial results information includes the adverse event information set forth in proposed § 11.48(a)(4) pursuant to section 402(j)(3)(I)(v) of the PHS Act, which indicates that the adverse event information included in the registry and results data bank under section 402(j)(3)(I) of the PHS Act ''is deemed to be clinical trial information included in [the] data bank pursuant to [section 402(j)(3)(C) of the PHS Act]'' (79 FR 69603). We received no comments on this definition.

We clarify in the final rule that the full set of data elements under § 11.48 must be submitted when results information is submitted for applicable clinical trials with a primary completion date on or after the effective date of the final rule, as discussed further in section IV.F. Effective Date, Compliance Date, and Applicability of Requirements in this part. For applicable clinical trials with a primary completion date before the effective date of the final rule, results information must be submitted as specified in sections 402(j)(3)(C) and 402(j)(3)(I) of the PHS Act. We also note that, under § 11.60, if a responsible party seeks to submit clinical trial results information voluntarily for an applicable clinical trial with a primary completion date on or after the effective date and for which clinical trial registration information is not submitted, clinical trial results information is defined to include the data elements in § 11.48 and the data elements in § 11.60(b)(2)(i)(B) or (c)(2)(i)(B), as applicable. Therefore, for the purposes of the final rule, ''clinical trial results information'' means ''the data elements that the responsible party is required to submit to *ClinicalTrials.gov,* as specified in sections 402(j)(3)(C) and 402(j)(3)(I) of the Public Health Service Act (42 U.S.C. 282(j)(3)(C) and (I)) or § 11.48, as applicable. If a responsible party submits clinical trial results information voluntarily for a clinical trial, clinical trial results information also means § 11.60(b)(2)(i)(B) or § 11.60(c)(2)(i)(B), as applicable.''

Comparison Group

In the NPRM, we defined ''comparison group'' in proposed § 11.10(a) to mean ''a grouping of human subjects in a clinical trial, other than an arm, that is used in analyzing the results data collected during the clinical trial'' (see 79 FR 69604). We received no comments on this definition and maintain the definition in the final rule, except the final rule definition clarifies that the grouping ''is or may be'' used in analyzing the results data.

We clarify that, in some trials, results data are not analyzed according to the arms to which human subjects were assigned; the data may be combined into other groupings for analysis. For example, in a cross-over study, human subjects in one arm of a trial may receive intervention X for a period of time followed by intervention Y, while human subjects in another arm of the trial may receive intervention Y for a period of time followed by intervention X. In such studies, outcome measures and adverse events are often analyzed and reported by intervention (*e.g.,* results for human subjects when receiving intervention X versus results for human subjects when receiving intervention Y), rather than by arm.[Ref. 84] When submitting results information to *ClinicalTrials.gov* under § 11.48, responsible parties must submit data in the way in which they were analyzed, whether by arm (as defined above) or by comparison group. We note that, in general, the set of comparison groups for a particular trial should account for all of the participants in the analysis.

Completion Date

In the NPRM, we defined ''completion date'' in § 11.10(a) to mean ''for a clinical trial, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated. In the case of clinical trials with more than one primary outcome measure with different completion dates, this term refers to the date upon which data collection is completed for all of the primary outcomes.''

As we explained in the NPRM, ''completion date'' is defined in section 402(j)(1)(A)(v) of the PHS Act as ''the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated'' (79 FR 69604). This term has particular significance because the responsible party is required to submit ''the expected completion date'' to *ClinicalTrials.gov* upon registration (see section 402(j)(2)(A)(ii)(I)(jj) of the PHS Act) and submit clinical trial results information for certain applicable clinical trials not later than 1 year after the earlier of the estimated or the actual completion date (see sections 402(j)(3)(E)(i)(I) and (II) of the PHS Act), unless the deadline is delayed or extended using one of the mechanisms described in § 11.44. For purposes of the proposed rule, we interpreted ''expected completion date'' in section 402(j)(2)(A)(ii)(I)(jj) of the PHS Act to be synonymous with ''estimated completion date'' in section 402(j)(3)(E)(i)(I) of the PHS Act.

The proposed rule adopted the statutory definition of ''completion date'' with respect to applicable clinical trials but proposed one modification. For a clinical trial that has multiple primary outcome measures each with a different date on which the final human subject is examined or receives an intervention for the purposes of final data collection, we proposed that ''completion date'' would refer to the date on which data collection is completed for all of the primary outcomes. The proposed rule also defined ''completion date'' for a pediatric postmarket surveillance of a device that is not a clinical trial as ''the date on which the final report summarizing the results of the pediatric postmarket surveillance is submitted to FDA.'' The proposed rule also noted that the current implementation of *ClinicalTrials.gov* uses the term ''primary completion date'' to refer to ''completion date,'' as defined in section 402(j)(1)(A)(v) of the PHS Act. This was done in the data bank to alert those submitting data to *ClinicalTrials.gov* under section 402(j) of the PHS Act that the definition of ''completion date'' differs from that of the term ''study completion date,'' which refers to the date on which the last subject makes the last visit as part of the clinical trial (commonly referred to as Last Patient Last Visit (LPLV)) and is also collected by *ClinicalTrials.gov* as an optional data element [Ref. 85]. We stated that

ClinicalTrials.gov would begin to use the term ''completion date'' once the final regulations take effect and that we would include a notice on *ClinicalTrials.gov* to alert responsible parties to this change in data element name.

We received comments on this definition. Commenters expressed concern about confusion and possible misinterpretation among responsible parties and the public about the definition. Many of these commenters suggested replacing ''completion date'' with ''primary completion date'' or ''primary outcome measure completion date,'' noting that *ClinicalTrials.gov* has used ''primary completion date'' since the enactment of FDAAA. Several other commenters requested that ''completion date'' be redefined to mean LPLV. In addition, several commenters supported the NPRM position that when there are multiple primary outcome measures, the completion date is interpreted as ''the date upon which data collection is completed for all of the primary outcomes.'' Two commenters also requested further clarification in the definition about the term's application to trials that are terminated, particularly when the decision to terminate occurs more than 1 year after the last previously enrolled subject reached the data collection point for a primary outcome measure, but before the enrollment goals are reached. One commenter requested clarification regarding cases in which sample analysis occurs after a patient's last visit. We did not receive any comments on the definition of ''completion date'' for a pediatric postmarket surveillance of a device that is not a clinical trial.

We generally maintain the definition of ''completion date'' in § 11.10(a) in the final rule because the statute explicitly defines the term in this way. We have made a minor modification, consistent with the statutory definition, to clarify that the term ''clinical trial'' includes an applicable clinical trial; we have also clarified that ''device'' means ''device product.'' However, we agree with the comments, so we are clarifying that ''completion date'' is synonymous with ''primary completion date,'' to avoid confusion among researchers and the public. We have revised the definition of ''completion date'' to state that for purposes of this part, the term ''completion date'' is referred to as ''primary completion date.'' We use the term ''primary completion date'' in this preamble and in the codified provisions. We also add to final § 11.10(a) the term ''primary completion date,'' which is defined as and refers to the definition of ''completion date.'' In addition, *ClinicalTrials.gov* will continue to use the term ''primary completion date'' and the related data element to refer to ''completion date,'' as defined in § 11.10(a) of the final rule. We believe that this approach balances the need to implement terms that are specifically defined by section 402(j) of the PHS Act while being responsive to commenters' concerns that the statutory definition of ''completion date'' differs from the way the term is commonly used by the clinical research community. This change will also help clarify the meaning of the statutory term for users.

Also, with regard to comments suggesting that ''completion date'' should mean LPLV, we note that adopting such an approach would be inconsistent with the statutory definition. However, we do add the Study Completion Date data element, which is currently an optional data element in *ClinicalTrials.gov*, as a required component of clinical trial registration information in the final rule, and we include a definition of ''study completion date'' in § 11.10(a). (See also the discussion of ''study completion date'' later in this preamble.) As supported by the commenters, we also maintain the definitional element for multiple primary outcomes as proposed, *i.e.,* that ''completion date'' (and ''primary completion date'') means the date on which data collection is completed for all of the primary outcomes. As explained in the NPRM, while this approach may delay the submission and public availability of clinical trial results information for the earliest primary outcomes, we expect any such delays to be minimal (79 FR 69604). Most clinical trials registered on *ClinicalTrials.gov* to date specify only a single primary outcome, and those with multiple primary outcomes have measurement time frames that are relatively close in time.

Moreover, this approach avoids cases in which the submission of clinical trial results information would be required before data collection has been completed for all of the primary outcomes in a clinical trial and before all of the results data for the primary outcomes have been ''unblinded,'' a situation that could threaten the scientific integrity of the clinical trial. While a responsible party could request a good-cause extension of the results information submission deadline in such a situation under § 11.44(e), the definition in the final rule should reduce the number of good-cause extension requests that responsible parties might be expected to file. Submission of results information for all primary outcomes at the same time will also aid in the interpretation of clinical trial results information by providing users of *ClinicalTrials.gov* with a more comprehensive set of results information from the clinical trial, rather than results information for only some of the primary outcomes.

In response to the commenters seeking clarification about the completion date for terminated clinical trials, we do not believe that any changes to the definition are needed. Under the definition of ''completion date,'' the completion date of a terminated trial is the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, which may be on or before the trial termination. By ''final subject,'' the definition means the last subject who was examined or received an intervention before the trial was terminated. We do not interpret this definition as meaning that all enrolled subjects must be examined or receive an intervention before the clinical trial is terminated in order for the trial to reach the completion date. As described in the discussion of § 11.48 in this preamble, the responsible party would provide the clinical trial results information that had been collected for those subjects who were examined or received the intervention up to the point of termination. In response to one commenter, we clarify that if an applicable clinical trial is terminated on a date that is after the last subject was examined or received an intervention for a primary outcome measure, the completion date would still be the date that the final subject was examined or received an intervention for the primary outcome before trial termination, regardless of when the decision to terminate was made and whether the enrollment goals were reached. In this scenario, it is possible that the decision to terminate the trial could occur after the standard submission deadline for study results information under § 11.44(a) (*i.e.,* 1 year after the primary completion date) or may occur during a period that is much less than 1 year after the primary completion date. We clarify that upon trial termination, a responsible party may submit a request demonstrating good-cause for extending the results information submission deadline as specified in § 11.44(e). Finally, in response to another comment, we do not agree that the date of sample analysis after a subject's last examination or receipt of the intervention should qualify as the ''completion date'' under the definition. We view sample analysis as a separate

step from data collection; moreover, including it in the definition of ''completion date'' would be inconsistent with the statutory definition. We also note that an analysis could be conducted months or even years after the last subject was examined or received an intervention, which could significantly delay the reporting of results information under § 11.44. We clarify that if there are extenuating circumstances that cause a delay in sample analysis that interferes with meeting the results information submission deadline specified in § 11.44, the responsible party may submit a request for extending the results information submission deadline as specified in § 11.44(e).

In § 11.10(a) of the final rule, we define ''completion date'' to mean ''for a clinical trial, including an applicable clinical trial, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated. In the case of clinical trials with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes. For a pediatric postmarket surveillance of a device product that is not a clinical trial, completion date means the date on which the final report of the pediatric postmarket surveillance of the device product is submitted to FDA. For purposes of this part, completion date is referred to as 'primary completion date.'''

Control or Controlled

In the NPRM, we defined ''control or controlled'' in § 11.10(a) to mean ''with respect to a clinical trial, that data collected on human subjects in the clinical trial will be compared to concurrently collected data or to non-concurrently collected data (*e.g.,* historical controls, including a human subject's baseline data), as reflected in the pre-specified primary or secondary outcome measures.'' ''Control'' and ''controlled'' are terms used in sections 402(j)(1)(A)(ii)(I) and (iii)(I) of the PHS Act as part of the definitions of ''applicable device clinical trial'' and ''applicable drug clinical trial,'' respectively. As we explained in the NPRM, the definition is consistent with (but broader than) FDA regulations that define the related concepts of ''adequate and well-controlled studies'' for drugs (21 CFR 314.126(b)(1) and (2)) and ''a well-controlled clinical investigation'' for devices (21 CFR 860.7(f)) (79 FR 69604). FDA has also adopted as guidance the ICH E10: Choice of Control Group and Related Issues in Clinical Trials, which describes considerations to be used in choosing a control group [Ref. 86]. In FDA regulations, the critical attribute of a well-controlled clinical trial, which is the intent of any controlled trial, is ''a design that permits a valid comparison with a control to provide a quantitative assessment'' of the effect of the investigational intervention (see 21 CFR 314.126(b)(2)). The FDA regulations recognize several types of concurrent controls (*e.g.,* active control) and the non-concurrent, historical control. This can refer to a control group for which data were collected at a different time or place but can also refer to a clinical trial in which subjects serve as their own controls (*e.g.,* the clinical trial measures change from baseline).

We explained in the NPRM that, for purposes of determining whether it is an applicable clinical trial subject to this part, the proposed definition of ''control or controlled'' would include any clinical trial with multiple concurrent arms (79 FR 69574 and 69605). In addition, we explained that some single-arm clinical trials would also be included in the definition. Such trials would include single-arm trials of FDA-regulated products that, as specified in their protocols, intend to evaluate an effect by comparing measures taken after an intervention to baseline measures taken from the participants prior to the intervention. Many of these studies have explicitly defined ''change from baseline'' measures identified in their protocols, *i.e.,* they are designed to compare a measure taken after an intervention to the participant's state prior to the intervention. Other single-arm trials that would be considered controlled include, for example, studies with an identified measure of ''response rate'' or measures in which the state prior to or without the intervention can be assumed (*e.g.,* studies in conditions that do not resolve over the time period studied without the intervention, such as certain types of cancer).

We proposed in § 11.10(b)(5) that the Study Design data element include, for single-armed studies, whether or not the clinical trial is controlled, as specified by the protocol or SAP. Accordingly, proposed § 11.28(a)(i)(v) would require that a responsible party that registers a single-arm trial provide this information. We also proposed in § 11.22(b) that a trial or study that was described accurately by the data elements listed in § 11.22(b)(1) or (2) would be considered to meet the definition of an applicable clinical trial. We invited comments on the proposed approach for identifying single-arm trials that would be considered controlled and on alternative ways to identify such trials (79 FR 69574). In particular, we invited comments on whether there are other specific, objective features of clinical trials that could serve as the basis for differentiating between single-arm studies that are and are not controlled. We also invited comments on and information about the types of single-arm trials that meet the other criteria for an applicable clinical trial and do or do not meet our proposed definition of ''controlled.''

We received several comments on the definition. One commenter supported the proposed definition, particularly including single-arm studies. Several commenters sought clarifications of the definition. Some commenters stated that *all* interventional studies in humans should be considered controlled for the purposes of the NPRM, including single-arm studies. Some commenters indicated that ambiguity around the definition of controlled could result in responsible parties making erroneous, subjective assessments and failing to register or submit information for certain trials. One of these commenters suggested that if the definition was not clarified to include all interventional studies, the rule should require a responsible party registering a single-arm study without a control to explain the trial's purpose, ethical approval, justification for the lack of a control, and knowledge to be obtained. Another commenter requested that the final rule amend the definition of ''controlled'' to include single-arm studies assessing changes from historical controls or baseline or, alternatively, revise the definition to clarify that all single-arm trials are considered controlled. Two commenters indicated that all single-arm interventional studies should be considered controlled by asserting that all such studies that otherwise meet the definitional criteria specified in proposed § 11.22(b) are considered to be applicable clinical trials. One of these commenters emphasized that single-arm studies should be considered controlled because they compare collected data to other information (*e.g.,* participant baseline data); the other commenter objected that the NPRM's proposal to distinguish controlled clinical trials from other trials is potentially confusing—especially in light of FDA's regulatory definition of ''[adequate and] well-controlled'' trials, and asserted that the ''controlled'' definition was

unnecessary for the applicable clinical trial determination. The commenter also noted that removing the ''controlled'' criterion and requiring results information reporting for all trials would better align the rule to the EU Clinical Trials Regulation. Finally, several commenters stated that no control groups should be allowed in clinical trials involving life-threatening conditions.

Other commenters asserted that the current definition of ''control or controlled'' is too broad. One stated that only multi-armed studies are controlled and that the standard use of the term ''controlled'' in the scientific community worldwide includes a comparison group. The commenter requested that for any single arm studies to be defined as controlled, a separate proposed rule with this approach should be issued for comment. Two commenters also expressed concerns that the meaning of ''controlled'' in the NPRM's definition differed from the FDA's definition of ''adequate and well controlled,'' and one suggested harmonizing the final rule with the EU Clinical Trials Regulation requirements for results information reporting but limiting the scope to ''adequate and well controlled'' studies under 21 CFR 314.126.

Another commenter suggested that the proposed definition may be too broad and that it could conceivably encompass any interventional study in which patient data are captured at baseline and post-intervention. The commenter suggested that to be included in the definition, a single-arm trial would need to be able to plausibly distinguish the effect of an intervention from other causes and, furthermore, that the definition could be revised to be limited to trials ''designed to permit a comparison of a test intervention with a control to provide a quantitative assessment of the effect of an intervention.'' The commenter also requested that NIH provide additional guidance for responsible parties on how to determine whether the study is controlled. Another commenter stated that single-arm phase 2 studies should be considered controlled only if they involve the comparison of primary and secondary endpoints and adverse events with a specific historical cohort. The commenter stated that a trial should not be considered controlled simply by the use of a pre-specified benchmark for the primary endpoint.

We have reconsidered our proposed approach based on the comments and determined that all interventional studies with pre-specified outcome measures should be considered controlled under the definition in the final rule, whether the trial has a single group of human subjects or involves two or more concurrent groups of human subjects. We agree with those comments suggesting that any single-arm interventional trial with pre-specified outcome measure(s) be considered controlled since it implicitly or explicitly compares the effect of the intervention to some other information (*e.g.,* patient baseline). Under our definition of ''interventional,'' the effect of the intervention on biomedical or other health-related outcomes is evaluated according to a research protocol. In order to assess the effect of the experimental intervention, plans for single-arm trials identify how the outcomes will be measured. Either explicitly or implicitly, the measured outcomes are compared with either the patients themselves prior to the intervention or historical data from other patients (or subjects). Therefore, a single-arm interventional study with pre-specified outcome measure(s) would always involve the use of some type of control to evaluate the intervention's effect.

This revised approach simplifies the rule's application by making it clearer, less subjective, and easier for responsible parties to implement. For example, the revised approach eliminates the need for a responsible party to rely on a subjective determination of ''controlled'' for single-group studies. In addition, the approach minimizes the chances of an applicable clinical trial not being registered (and subsequently not reporting results information). The approach also harmonizes the definition of ''control or controlled'' for trials of drugs and device products. Importantly, we believe the approach supports the purpose of the provisions of section 402(j) of the PHS Act to make more information about clinical trials available to the public. Accordingly, § 11.10(a) of the final rule defines ''control or controlled'' to include not only concurrent control groups, but also non-concurrent controls, which would include all single-arm clinical trials with pre-specified outcome measures. In addition, the following clarification is added to the end of the definition: ''For purposes of this part, all clinical trials with one or more arms and pre-specified outcome measure(s) are controlled.'' We wish to note, however, that although in certain circumstances some types of expanded access use under section 561 of the FD&C Act arguably might fall within this definition, as discussed above, expanded access use is not considered to fall within the definition of ''applicable drug clinical trial.''

The definition of ''control or controlled'' in the final rule is consistent with the types of controls recognized by FDA and the ICH E10 guidance (*i.e.,* recognition of both concurrent and non-concurrent controls) [Ref. 86]. The definition, however, is necessarily broader than the definition of ''adequate and well-controlled'' used in FDA regulations and the ICH E10 guidance because the purpose of this term, as used in this rule, is different from the more limited circumstances in which use of a non-concurrent control constitutes an ''adequate and well-controlled'' clinical trial, *i.e.,* one that might serve to support marketing authorization. Our definition does not reflect a consideration of the adequacy or appropriateness of the control or the adequacy of the study design, *e.g.,* whether adequate steps were taken to minimize bias. Because the transparency goals underlying this final rule also apply to clinical trials that may not be considered ''adequate and well-controlled'' under FDA regulations, we conclude that responsible parties are required to register and submit results information for such trials. Therefore, the definitions of ''applicable device clinical trial'' and ''applicable drug clinical trial'' include clinical trials with pre-specified outcome measures, whether using concurrent or non-concurrent controls, regardless of whether they would be considered ''adequate and well-controlled.''

Device

In the NPRM, we defined ''device'' in § 11.10(a) to mean ''a device as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(h))'' as specified in section 402(j)(1)(A)(vi) of the PHS Act (see 79 FR 69668). We received no comments on this definition, and we retain it without modification in the final rule.

Director

In the NPRM, we defined ''Director'' in § 11.10(a) to mean the NIH Director or any official of the NIH to whom the NIH Director delegates authorities granted in 42 U.S.C. 282(j) (see 79 FR 69668). We received no comments on this definition, and we maintain it in the final rule, except that we clarify the statutory reference as ''section 402(j) of the Public Health Service Act (42 U.S.C. 282(j)).''

Drug

In the NPRM, we defined ''drug'' in § 11.10(a) to mean ''a drug as defined in

section 201(g) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(g)) or a biological product as defined in section 351 of the Public Health Service Act (42 U.S.C. 262),'' as specified in section 402(j)(1)(A)(vii) of the PHS Act (see 79 FR 69668). We received no comments on this definition, and we retain it without modification in the final rule.

Enroll or Enrolled

In the NPRM, we defined ''enroll or enrolled'' in § 11.10(a) to mean ''a human subject's agreement to participate in a clinical trial, as indicated by the signing of the informed consent document(s).'' As we explained, ''enroll or enrolled'' is a term used in section 402(j)(1)(A)(viii)(I) of the PHS Act as part of the definition of ''[o]ngoing'' and in 402(j)(2)(C)(ii) of the PHS Act as one of the criteria used to establish the deadline by which a responsible party is required to submit clinical trial registration information (79 FR 69605).

We received comments on this definition. Several commenters asserted that the proposed definition of ''enrolled'' may be inconsistent with the way the term is used for presenting information about device studies in the Summary of Safety and Effectiveness or the 510(k) Summary, which are publicly available on FDA's Web site and to which *ClinicalTrials.gov* is required to link. The commenters stated that device trials can include subjects who, according to the trial design, provide consent for screening but enroll only those subjects who subsequently pass screening. The commenters asserted that the definition of ''enrolled'' proposed in the NPRM would require the inclusion of those subjects who provide consent for screening but do not pass screening, thereby resulting in an inconsistency in enrollment numbers reported on the *ClinicalTrials.gov* Web site and FDA's 510(k) Summary or Summary of Safety and Effectiveness, which would lead to confusion.

We acknowledge that there may be differences in the numbers of participants who sign an informed consent, are screened for participation, and are eligible to participate in the clinical trial. Therefore, we clarify that the definition of ''enroll or enrolled'' does not include ''potential subjects who are screened for the purpose of determining eligibility for the trial but do not participate in the trial, unless otherwise specified by the protocol.''

We note that, in some cases, there may be a separate informed consent document for trial screening and trial participation; the signing of the latter aligns with the proposed definition. We clarify that when there is only one informed consent for both trial screening and trial participation, and it is signed prior to participant screening, a participant is not considered enrolled until he or she has met all the eligibility criteria assessed during screening, unless the participant is considered enrolled specifically by the protocol. We clarify that for the purposes of the registration submission requirement in § 11.24, clinical trial registration information is required to be submitted no later than 21 calendar days after the first subject signs the informed consent form for trial participation. When there is only one informed consent for both trial screening and trial participation, we clarify that clinical trial registration information is required to be submitted pursuant to § 11.24 no later than 21 calendar days after the first subject signs the informed consent form and begins trial participation, in accordance with the protocol.

Commenters also stated that the definition of ''enroll or enrolled'' should be expanded to include ''unless specifically defined differently in the protocol.'' The commenters asserted that not all studies consider the signing of informed consent to be the point of enrollment, and that the signing of informed consent may not be required. Moreover, based on these particular comments, we believe the wording of the proposed definition may inadvertently suggest that a written signature is the only acceptable confirmation of a subject's consent to participate. We have modified the definition to account for situations in which consent is provided by a subject's legally authorized representative (*e.g.,* a family member) because the subject is not able to provide informed consent because of, for example, mental incapacity. To address these and the previous comments, we are revising the definition of ''enroll or enrolled'' to mean ''a human subject's, or their legally authorized representative's, agreement to participate in a clinical trial following completion of the informed consent process as required in 21 CFR part 50 and/or 45 CFR part 46, as applicable. For the purposes of this part, potential subjects who are screened for the purpose of determining eligibility for the trial, but do not participate in the trial, are not considered enrolled unless otherwise specified by the protocol.''

Human Subjects Protection Review Board

In the NPRM, we defined ''human subjects protection review board'' in § 11.10 to mean an ''institutional review board (IRB) as defined in 21 CFR 50.3 and 45 CFR 46.102 (or any successor regulation), as applicable, or equivalent independent ethics committee that is responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical investigation and is adequately constituted to provide assurance of that protection.'' We proposed to include this definition to clarify the scope of the review boards for which Human Subjects Protection Review Board Status must be submitted under § 11.28 (79 FR 69605). We did not receive any comments on this definition, but for further clarity we are modifying the definition in the final rule to mean ''an institutional review board (IRB) as defined in 21 CFR 50.3 or 45 CFR 46.102, as applicable, that is responsible for assuring the protection of the rights, safety, and well-being of human subjects involved in a clinical trial and is adequately constituted to provide assurance of that protection. An IRB may also be known as an 'independent ethics committee.' '' For clinical trials conducted in the United States or under an IND or IDE, the term ''human subjects protection review board'' means an IRB, as defined in the cited regulations issued by FDA and HHS. For clinical trials conducted outside the United States or which are otherwise not subject to the FDA and/or HHS regulations for IRBs, the term refers to other independent ethics committees that are responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical investigation and are adequately constituted to provide assurance of that protection. This phrasing is consistent with, but not identical to, the definition of the term ''independent ethics committee'' in FDA regulations for INDs (see 21 CFR 312.3). It is also consistent with longstanding use of the term ''human subjects protection review board'' on *ClinicalTrials.gov*, which instructed registrants to provide information about ''[a]ppropriate review boards[, including] an Institutional Review Board, an ethics committee or an equivalent group that is responsible for review and monitoring of this protocol to protect the rights and welfare of human research subjects'' [Ref. 85].

Interventional

In the NPRM, we defined ''interventional'' in § 11.10 to mean ''with respect to a clinical study or a clinical investigation, that participants are assigned prospectively to an intervention or interventions according

to a protocol to evaluate the effect of the intervention(s) on biomedical or other health related outcomes.'' The term ''interventional'' is used in § 11.22 as one of the elements (*i.e.,* interventional Study Type) used to determine whether a clinical study or a clinical investigation is an applicable clinical trial that is required to be registered. We proposed to define this term to distinguish interventional studies from observational studies, as those terms are used in the clinical research community (79 FR 69605). Observational studies consist of medical research in which the investigator does not assign human subjects to interventions. Observational studies include prospective cohort studies in which individuals received interventions as part of their medical care, after which the investigator studies prespecified outcomes to examine the impact of those interventions. Observational studies also include retrospective reviews of patient medical records or relevant literature. In contrast, in interventional studies, a researcher assigns subjects to specific interventions (*e.g.,* placebo, routine medical care, or no intervention) according to a study protocol for the purposes of the investigation. We explain in the preamble discussion for the definition of ''protocol'' in § 11.10(a) of the final rule that a less formal research plan would also be considered a protocol for the purposes of this part, including the definition of ''interventional.''

We received comments addressing the definition. Several commenters requested that the definition of ''interventional'' include a study (other than an observational study) of any approved or unapproved drug, biologic, device, radionuclide, or any other substance that is introduced into the human body during the study's experimental phase (*i.e.,* phase 0 through phase 4). As described in the preamble discussion for the definition of ''applicable drug clinical trial,'' phase 0 and 1 studies are not included in the applicable clinical trials that must be registered under § 11.22, but such studies may still meet the definition of ''interventional.'' The definition of ''interventional'' in the NPRM is generally consistent with what the commenters recommended, except that we provided more detail to help responsible parties apply the definition, including that interventional studies are those that: (1) Prospectively assign participants to an intervention, (2) do so according to a protocol, and (3) evaluate the intervention's effect on biomedical or other health-related outcomes. The commenters also described various types of observational studies that they believed would be excluded from this definition, including studies evaluating patients' responses independent of the actual ongoing clinical trial or other activities that have no direct interaction with the human body, but little detail was provided about these examples. However, we note that certain studies described by commenters did seem to fit the definition of ''observational'' (but not ''interventional'') because assignment to the intervention was based on routine care instead of a protocol, such as a study of patients receiving an intervention as part of routine medical care to assess any correlation between certain biomarkers and the intervention's effect.

Similarly, a commenter requested that the final rule clarify aspects of the ''prospectively assigned to the intervention per protocol'' component of the definition. The commenter asked specifically whether an intervention would be considered ''prospectively assigned'' if the administration of the test article began before subjects participated in the study (*i.e.,* the study assessed the effect of a therapy that was ongoing at the time of subject recruitment) and whether a drug provided as part of routine medical care would meet the requirement of being ''prospectively assigned'' if provision of the drug it occurred after subjects become research participants. In general, the timing of the intervention's administration in these cases would not be considered as relevant as how decisions for the participant to receive the intervention were made. If the decision for the participant to receive the intervention was based on routine medical care and not on assignment according to a protocol or research plan, the study would generally not be considered interventional. We note that there may be other aspects of the study design that were not described by the commenter that would otherwise cause the study to meet the definition of ''interventional'' (*e.g.,* other interventions are simultaneously being evaluated for their effect on outcomes related to human health, such as an IVD test). We also clarified in the NPRM that a study would meet the definition of ''interventional'' if assignment to the intervention is determined by the researcher based on a formal protocol or research plan, even when the medical products being studied are being used in a manner considered to be the standard of care (79 FR 69605). We also note, as discussed in Section V, that we will issue more guidance in the future on examples of applicable clinical trials for the checklist described in § 11.22.

Another comment requested clarification of the meaning of ''biomedical or other health-related outcomes.'' We believe our explanation of ''a prospective clinical study of health outcomes'' for the definition of ''applicable device clinical trial'' is informative. In the NPRM, we explained that a ''prospective clinical study of health outcomes'' is a ''clinical study in which the primary objective is to evaluate a defined clinical outcome related to human health'' (79 FR 69599). For example, a clinical study of a diagnostic device (such as an IVD) in which the primary purpose is to evaluate the ability of the device to make a diagnosis of a disease or condition is related directly to human health and, therefore, would be considered a clinical study of health outcomes for purposes of this rule.

After considering these comments, we maintain the definition of ''interventional'' in the final rule to mean ''with respect to a clinical study or a clinical investigation, that participants are assigned prospectively to an intervention or interventions according to a protocol to evaluate the effect of the intervention(s) on biomedical or other health-related outcomes.'' For the purposes of this part, we use the term ''clinical trial'' to refer to interventional studies to the exclusion of observational studies. (See the definition of ''clinical trial.'') The term ''interventional'' is one of the responses that can be submitted as part of the Study Type data element that is included as clinical trial registration information under § 11.28 and defined in § 11.10. Responsible parties must indicate whether a study being registered is ''interventional'' or ''observational'' or is expanded access (see the discussion below). A study that is designated as ''interventional'' can be an applicable clinical trial if it meets the other criteria for an applicable clinical trial that are specified in this part. (See the definitions of ''applicable device clinical trial'' and ''applicable drug clinical trial.'') A study that is designated ''observational'' can be an applicable clinical trial only if it is a pediatric postmarket surveillance of a device product as defined in this part. (See the definition of ''pediatric postmarket surveillance of a device product.'')

Investigational Device Exemption (IDE)

In the NPRM, we defined ''Investigational Device Exemption (IDE)'' in § 11.10(a) to have ''the meaning given in 21 CFR 812, or any

successor regulation'' (see 79 FR 69668). We did not receive any comments on this definition, and we maintain it in the final rule.

Investigational New Drug Application (IND)

In the NPRM, we defined ''Investigational New Drug Application (IND)'' in § 11.10(a) to have ''the meaning given in 21 CFR 312.3, or any successor regulation'' (see 79 FR 69668). We did not receive any comments on this definition, and we maintain it in the final rule.

NCT Number

In the NPRM, we defined ''NCT number'' in § 11.10(a) to mean ''the unique identification code assigned to each record in *ClinicalTrials.gov*, including a record for an applicable clinical trial, a clinical trial, or an expanded access program'' (79 FR 69606). ''NCT number'' refers to the term ''National Clinical Trial number'' used in section 402(j)(2)(B)(i)(VIII) of the PHS Act. We did not receive any comments on this definition, and we maintain it in the final rule.

Since its launch in 2000, *ClinicalTrials.gov* has assigned each submitted clinical trial record a unique identifier once quality review procedures have been completed for the submitted information. While the identifier was originally called a ''National Clinical Trial number,'' that nomenclature was soon changed to ''NCT number'' in recognition of the fact that *ClinicalTrials.gov* receives clinical trial information about trials being conducted in countries other than the United States and accommodates the registration of clinical studies other than clinical trials (*e.g.,* observational studies). NCT numbers are used in many contexts to refer to clinical trial records or other types of records (*e.g.,* observational studies, expanded access programs) that are accepted by *ClinicalTrials.gov*. Under the ICMJE registration policy, for example, journals publishing original papers on the results of clinical trials require the authors to include in their manuscripts a unique identification number assigned by a recognized clinical trial registry as evidence that the trial has been registered in compliance with the ICMJE policy [Ref. 1, 2]. For trials registered on *ClinicalTrials.gov*, this unique identifier is the NCT number. When published in journal articles, NCT numbers are also included in the Medical Literature Analysis and Retrieval System Online records and are searchable through PubMed [Ref. 87]. Furthermore, section 402(j)(5)(B) of the PHS Act specifies that ''such certification [to accompany drug, biological product, and device applications or submissions to FDA] shall include the appropriate National Clinical Trial control numbers.''

Ongoing

In the NPRM, we defined ''ongoing'' in § 11.10(a) to mean ''with respect to a clinical trial of a drug or a device and to a date, that one or more human subjects is enrolled in the clinical trial, and the date is before the completion date of the clinical trial.'' As we explained in the NPRM, this proposed definition is the same as the statutory definition, except the term ''human subjects'' has been substituted for the term ''patients'' that is used in section 402(j)(1)(A)(viii) of the PHS Act (79 FR 69606). The reason for this change is that clinical trials may include healthy volunteers as well as human subjects who might be considered ''patients.'' With respect to a pediatric postmarket surveillance of a device product, we defined the term ''ongoing'' to mean ''a date between the date on which FDA approves the plan for conducting the surveillance and the date on which the final report is submitted to FDA.''

We received comments addressing this definition. Two commenters asked that we clarify the definition and asserted that researchers consider trials to be ongoing even after the statutorily defined completion date. We note, though, that a trial cannot be considered ongoing in accordance with the statutory definition if the date is on or after the primary completion date (see the explanation above with regard to use of the term ''primary completion date''). Therefore, on or after the primary completion date, trials would not be considered ongoing for the purposes of this part and the applicable requirements.

After considering these comments, we maintain the NPRM definition of ''ongoing,'' except that (as discussed previously) we replace ''completion date'' with ''primary completion date,'' consistent with the definition of ''completion date'' in this section, and we clarify that ''drug'' means ''drug product'' and ''device'' means ''device product.'' We define ''ongoing'' in the final rule to mean ''with respect to a clinical trial of a drug product or a device product and to a date, that one or more human subjects is enrolled in the clinical trial, and the date is before the primary completion date of the clinical trial. With respect to a pediatric postmarket surveillance of a device product, ongoing means a date between the date on which FDA approves the plan for conducting the surveillance and the date on which the final report is submitted to FDA.''

Outcome Measure

In the NPRM, we defined ''outcome measure'' in § 11.10(a) to mean ''a pre-specified measurement that will be used to determine the effect of experimental variables on the human subjects in a clinical trial.'' As we explained in the NPRM, the experimental variables may be the specific intervention(s) used in the clinical trial or other elements of the clinical trial that vary between arms, *e.g.,* diagnostic or other procedures provided to participants in different arms (79 FR 69606). One commenter supported this definition.

We maintain the definition of ''outcome measure'' in the final rule except we make conforming changes to two elements, *i.e.,* we say ''an experimental variable'' and ''on the human subject(s)'' to be consistent with other definitions in the rule. In this part, ''outcome measure'' refers to measurements observed or collected from those human subjects who are enrolled in the clinical trial. Although it is not uncommon to compare data derived from human subjects enrolled in a clinical trial with data derived from other sources (*e.g.,* literature, other clinical trials), we believe that only measurements taken from participants in the clinical trial of interest should be submitted as results information to *ClinicalTrials.gov*. In our view, comparisons of such data with results data derived from other sources are more appropriately described in forums other than *ClinicalTrials.gov* (*e.g.,* journal articles) where the other necessary information about the comparator group can be provided. Clinical trial information submitted to *ClinicalTrials.gov* would generally not include information or data about the human subjects studied in another clinical trial (*i.e.,* the clinical trial record would not contain baseline and demographic information about them, nor would it describe how they were allocated to arms of the clinical trial to receive interventions). (See the definitions of ''primary outcome measure'' and ''secondary outcome measure.'')

Pediatric Postmarket Surveillance of a Device Product

Section 402(j)(1)(A)(ii)(II) of the PHS Act defines the term ''applicable device clinical trial'' to include ''a pediatric postmarket surveillance as required under section 522 of the [FD&C] Act.'' The term ''[a]pplicable device clinical trial'' includes ''a pediatric postmarket surveillance as required under[section

522 of the FD&C Act].'' In the NPRM, we defined the term ''pediatric postmarket surveillance of a device'' in § 11.10(a) to mean ''the active, systematic, scientifically valid collection, analysis, and interpretation of data or other information conducted under section 522 of the [FD&C] Act about a marketed device that is expected to have significant use in patients who are 21 years of age or younger at the time of diagnosis or treatment (see 79 FR 69606). A pediatric postmarket surveillance of a device may be, but is not always, a clinical trial.'' Pursuant to section 522 of the FD&C Act, FDA defines the term ''postmarket surveillance'' as ''the active, systematic, scientifically valid collection, analysis, and interpretation of data or other information about a marketed device'' (see 21 CFR 822.3(h)). In Title III of FDAAA, Congress directed that the term ''pediatric,'' when used with respect to devices, refers to patients 21 and younger (see Title III of FDAAA (''Pediatric Medical Device Safety and Improvement Act of 2007''), amending section 520(m) of the FD&C Act).

FDA may order a pediatric postmarket surveillance of a device under section 522 of the FD&C Act for any class II or class III device, as defined by 21 U.S.C. 360c(a) and 21 CFR 860.3, meeting any of the following criteria: (1) Its failure would be reasonably likely to have serious adverse health consequences, (2) it is expected to have significant use in pediatric populations, (3) it is intended to be implanted in the body for more than 1 year, or (4) it is intended to be a life-sustaining or life-supporting device outside a device user facility (see 21 U.S.C. 360l(a)). Pediatric postmarket surveillances under section 522 of the FD&C Act can take various forms, including a detailed review of the complaint history and the scientific literature, non-clinical testing, observational studies, and controlled clinical trials.

Because section 402(j)(1)(A)(ii)(II) of the PHS Act defines the term ''applicable device clinical trial'' to include pediatric postmarket surveillances of a device, such surveillances must be registered, and clinical trial results information must be submitted for them. The final rule's approach for applying the registration requirements to a pediatric postmarket surveillance of a device that is not a clinical trial is described in § 11.28(b), and the final rule's approach for applying the results information submission requirements to a pediatric postmarket surveillance of a device that is not a clinical trial is described in § 11.48(b). A pediatric postmarket surveillance of a device that is a clinical trial is subject to the general requirements of this final rule, including the clinical trial registration and results information submission requirements in §§ 11.28(a) and 11.48(a), respectively.

We received no comments on this proposed definition, and we maintain it in the final rule. However, for clarity and consistency, ''device'' is changed to ''device product.'' For completeness, we also include the applicable U.S.C. statutory citation in the definition.

Primary Completion Date

As discussed above, based on comments we received, we have decided to maintain the proposed rule's definition of ''completion date'' in § 11.10(a) of the final rule but, in order to prevent confusion among researchers and the public, we use the term ''primary completion date'' in this preamble and the codified provisions. Therefore, we add the term ''primary completion date'' to § 11.10(a), define it as ''completion date,'' and refer to the definition of that term.

Primary Outcome Measure(s)

In the NPRM, we defined ''primary outcome measure(s)'' in § 11.10(a) to mean ''the outcome measure(s) of greatest importance specified in the protocol, usually the one(s) used in the power calculation. Most clinical trials have one primary outcome measure, but a clinical trial may have more than one.'' The NPRM also noted that, for the purpose of this part, ''primary outcome'' has the same meaning as ''primary outcome measure'' (79 FR 69606). The term ''primary outcome measure(s)'' is used, but not defined, in section 402(j) of the PHS Act. Section 402(j)(2)(A)(ii)(I)(ll) of the PHS Act expressly requires primary outcome measures to be submitted as a clinical trial registration information data element. In addition, section 402(j)(1)(A)(v) of the PHS Act defines the completion date in relation to the ''final collection of data for the primary outcome.'' Primary outcome measure(s) is also expressly required as a clinical trial results information data element by section 402(j)(3)(C)(ii) of the PHS Act. As we explained in the NPRM, we believe this approach enables users of *ClinicalTrials.gov* to identify the pre-specified primary outcome measure(s) for the clinical trial submitted as part of the clinical trial registration information and to examine the results data collected for those outcome measures and submitted to the data bank as part of clinical trial results information. (See also the discussion in Sections IV.B.4 and IV.C.4 of this preamble regarding primary outcome measure as a clinical trial registration information data element in § 11.28(a)(2)(i)(W) and as a clinical trial results information data element in § 11.48(a)(3).) We received one comment in support of the proposed definition. We maintain the definition in the final rule, except, for greater clarity about the definition's scope, we add the phrase ''for purposes of this part.''

Principal Investigator

In the NPRM, we defined ''principal investigator'' in § 11.10 to mean ''the individual who is responsible for the scientific and technical direction of the study.'' As we explained, ''principal investigator'' is a term used in the definition of ''responsible party'' in section 402(j)(1)(A)(ix) of the PHS Act and in the description of the Certain Agreements results data element in section 402(j)(3)(C)(iv) of the PHS Act, but the term itself is not defined in section 402(j) of the PHS Act (79 FR 69607). The definition uses terminology derived from 42 CFR 52.2, which defines ''principal investigator'' in the context of an NIH grant as ''the individual(s) judged by the applicant organization to have the appropriate level of authority and responsibility to direct the project or program supported by the grant and who is or are responsible for the scientific and technical direction of the project.'' We did not include the phrases ''applicant organization'' and ''project or program supported by the grant,'' which are specific to NIH-funded grants, because these references would not necessarily apply to applicable clinical trials that are funded by industry or other non-governmental organizations. We used the term ''study'' in place of ''project'' because the projects of relevance to this rule would be clinical studies, whether clinical trials or pediatric postmarket surveillances of a device. We also made it clear that the definition applies to only a single individual. This is consistent with our interpretation that there cannot be more than one responsible party for a clinical trial that is subject to section 402(j) of the PHS Act. We would expect a principal investigator to have full responsibility for the treatment and evaluation of human subjects in the study and for the integrity of the research data for the full study. In keeping with this approach, an investigator for an individual site in a multi-site clinical trial would not be considered the principal investigator unless he or she also has overall responsibility for the clinical trial at all sites at which it is being conducted.

This interpretation is consistent with the requirement in section 402(j)(1)(A)(ix) of the PHS Act that a principal investigator may be designated by the sponsor as a responsible party only if he or she is responsible for conducting the trial, has access to and control over the data from the clinical trial, has the right to publish the clinical trial results, and has the ability to meet all the requirements for the submission of clinical trial information under section 402(j) of the PHS Act and this part.

We received comments on this proposed definition. Commenters requested that we make the proposed definition of ''principal investigator'' consistent with relevant FDA definitions. ''Principal investigator'' is not defined in FDA regulations or HHS ''Common Rule'' regulations (45 CFR part 46). However, FDA regulations in 21 CFR part 312 define ''investigator'' as ''an individual who actually conducts a clinical investigation (*i.e.,* under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team'' (see 21 CFR 312.3(b)). Other FDA regulations in 21 CFR parts 50, 56, and 812 define ''investigator'' similarly. The commenters noted that for large academic consortium studies, there may be an investigator who is responsible for the study's scientific and technical direction and who is commonly referred to as the ''overall principal investigator'' or ''study director.'' As the commenters noted, FDA regulations do not define ''principal investigator,'' and our proposed definition is for the purposes of this rule.

We do not believe that the proposed definition is inconsistent with FDA's definition of an ''investigator.'' As we explained above, the definition is based on the NIH regulation applying to grants (42 CFR 52.2), with which academic medical centers should be familiar. We clarify that in the commenters' examples, the ''overall principal investigator'' or ''study director'' responsible for the study's overall scientific and technical direction would be considered the ''principal investigator'' for the purpose of this part. If there are clinical trials for which there is more than one individual whom the sponsor considers to be a principal investigator for the overall study, the sponsor may designate only one of these principal investigators as the responsible party. Another commenter also stated that the definition should include a qualifier to designate the principal investigator for the overall study (with multiple sites) or an individual site.

After considering these comments, we modify the definition of ''principal investigator'' to clarify that the principal investigator is responsible for the overall study (as distinguished from the individual study sites). The definition of ''principal investigator'' in the final rule means ''the individual who is responsible for the overall scientific and technical direction of the study.'' We note that the principal investigator of a grant awarded by a Federal Government agency that funds a clinical trial may not necessarily be the principal investigator for that clinical trial for the purposes of this part. For example, for the purposes of grant funding, NIH defines ''program director/principal investigator'' in part as ''[t]he individual(s) designated by the applicant organization to have the appropriate level of authority and responsibility to direct the project or program to be supported by the award.'' [Ref. 87a]. Such an individual may or may not be ''the individual who is responsible for the overall scientific and technical direction of the study'' as defined in § 11.10(a) of this regulation.

In addition, the principal investigator on a Federal grant who has responsibility for only one site of a multi-site clinical trial (see, for example, 42 CFR 52.2) would neither have the requisite responsibility for conducting the entire trial nor the requisite access to data from all sites involved in the clinical trial, both of which are required by section 402(j) of the PHS Act and this part in order to meet the definition of ''responsible party.'' Accordingly, the principal investigator on such a grant could not be designated by the sponsor to be the responsible party for the purposes of registering a clinical trial and submitting clinical trial results information under section 402(j) of the PHS Act and this part.

Protocol

In the NPRM, we defined ''protocol'' in § 11.10(a) to mean ''the written description of the clinical trial, including objective(s), design, and methods. It may also include relevant scientific background and statistical considerations.'' As we explained in the NPRM, the protocol is the document that describes the design of a clinical trial. It may be, and frequently is, amended after a clinical trial has begun (79 FR 69607). This definition is derived from ICH E6(R1): Good Clinical Practice: Consolidated Guideline [Ref. 81] which defines the term as ''[a] document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents.'' The protocol generally addresses major statistical considerations, such as the number of human subjects required to provide adequate statistical power, but it may or may not include detailed information about the specific statistical analyses to be performed as part of the clinical trial. Such information may be contained in a separate SAP. We received no comments on this definition, and we maintain it in the final rule. We note, for the purposes of this part, that the written description may vary in the degree of detail, structure, or format. This clarification is relevant for other definitions in this part that include the ''protocol'' component, including the definitions for ''clinical trial'' and ''interventional.''

Responsible Party

In the NPRM, we defined ''responsible party'' in § 11.10(a) to mean ''with respect to a clinical trial, (i) the sponsor of the clinical trial, as defined in 21 CFR 50.3 (or any successor regulation); or (ii) the principal investigator of such clinical trial if so designated by a sponsor, grantee, contractor, or awardee, so long as the principal investigator is responsible for conducting the trial, has access to and control over the data from the clinical trial, has the right to publish the results of the trial, and has the ability to meet all of the requirements under this part for the submission of clinical trial information. For a pediatric postmarket surveillance of a device that is not a clinical trial, the responsible party is the entity whom FDA orders to conduct the pediatric postmarket surveillance of a device.'' As we explained, ''responsible party'' is the term defined in section 402(j)(1)(A)(ix) of the PHS Act and used in section 402(j) of the PHS Act to refer to the entity or individual who is responsible for registering a clinical trial or a pediatric postmarket surveillance of a device that is not a clinical trial, for submitting clinical trial results information to *ClinicalTrials.gov*, and for updating all submitted clinical trial information (79 FR 69607). We received no comments on this definition, and we maintain it in the final rule. We have, however, made a minor formatting change and grammatical correction (changing ''whom'' to ''who''). As we have elsewhere, we also now use the term ''device product.'' The procedures for determining which individual or entity meets the definition of

''responsible party'' are specified in § 11.4(c) and described in Section IV.A.2 of this preamble. We address the comments on these procedures in that section.

Secondary Outcome Measure(s)

In the NPRM, we defined ''secondary outcome measure'' in § 11.10(a) to mean ''an outcome measure that is of lesser importance than a primary outcome measure, but is part of a pre-specified plan for evaluating the effects of the intervention or interventions under investigation in a clinical trial.'' As we explained in the NPRM, a ''clinical trial may have more than one secondary outcome measure'' (79 FR 69607). We also noted that for the purpose of this part, ''secondary outcome'' has the same meaning as ''secondary outcome measure.'' ''Secondary outcome measure'' is a term used, but not defined, in section 402(j) of the PHS Act. Section 402(j)(2)(A)(ii)(I)(ll) of the PHS Act expressly requires secondary outcome measures to be submitted as a clinical trial registration information data element, as a component of the outcome measures data element. In addition, secondary outcome measure(s) is also expressly required as a clinical trial results information data element by section 402(j)(3)(C)(ii) of the PHS Act. As we said, we believe this structure enables users of *ClinicalTrials.gov* to identify the pre-specified secondary outcome measures for the clinical trial submitted as part of the clinical trial registration information and to examine the results data collected for those outcome measures and submitted to the data bank as part of clinical trial results information. We also pointed out that the definition is consistent with the WHO Trial Registration standard and ICMJE registration policies [Ref. 2, 73].

We received comments on this definition. One commenter supported this definition. We also heard from others that we should clarify whether any outcomes that are not part of the SAP, or are indicated to be tertiary or exploratory, are secondary outcome measures. We consider secondary outcome measures to be those outcome measures (other than the primary outcome measures) that are not considered exploratory or tertiary and for which there is a specific analysis plan. In general, the analysis plan would be specified in the protocol or SAP, but protocols do not always contain detailed information about statistical analyses, and SAPs may not be complete at the time a trial is registered. Therefore, the plan to analyze the secondary outcome measures may only be expressed in other formal trial documentation (*e.g.,* a grant application, contract, or published journal article). Therefore, in response to these comments, we confirm that outcome measures that are not part of an analysis plan, or are indicated to be exploratory or tertiary, are lower-level outcome measures and not secondary outcome measures. These lower-level outcome measures are not required to be submitted to *ClinicalTrials.gov*, but the information may be submitted voluntarily. (See the discussions in Sections IV.B.4 and IV.C.3 of this preamble, respectively, regarding secondary outcome measure(s) as a clinical trial information data element to be submitted at the time of registration, pursuant to § 11.28(a)(2)(i)(X), and at the time of results information submission, pursuant to § 11.48(a)(3).) After consideration of these comments, we clarify that a pre-specified exploratory or tertiary measure is not considered a secondary outcome. The definition of ''secondary outcome measure(s)'' in § 11.10(a) of this final rule is ''an outcome measure that is of lesser importance than a primary outcome measure, but is part of a pre-specified analysis plan for evaluating the effects of the intervention or interventions under investigation in a clinical trial and is not specified as an exploratory or other measure. A clinical trial may have more than one secondary outcome measure.'' For the purpose of this part, ''secondary outcome'' has the same meaning as ''secondary outcome measure.'' We include the phrase ''and is not specified as an exploratory or other measure'' to be clear that a pre-specified exploratory or other measure is not considered a secondary outcome measure.

Secretary

In the NPRM, we defined ''Secretary'' in § 11.10(a) to mean ''the Secretary of Health and Human Services or any other official(s) to whom the Secretary delegates authority contained in 42 U.S.C. 282(j)'' (see 79 FR 69669). We received no comments on this definition. We maintain it, except that we make clear that that the Secretary's authority is contained in ''section 402(j) of the Public Health Service Act (42 U.S.C. 282(j).''

Serious Adverse Event

In the NPRM, we defined ''serious adverse event'' in § 11.10(a) to mean ''an adverse event that results in any of the following outcomes: Death, a life-threatening adverse event as defined in 21 CFR 312.32 (or any successor regulation), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the human subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of a substance use disorder.'' As we explained in the NPRM, ''serious adverse event'' is a term used, but not defined, in section 402(j)(3)(I) of the PHS Act (79 FR 69608). Section 402(j)(3)(I)(iii)(I) of the PHS Act requires the submission to *ClinicalTrials.gov* of specific information about ''anticipated and unanticipated serious adverse events'' for applicable clinical trials of drugs as well as devices.

We received comments on this definition. Commenters suggested that the adverse event reporting requirements for devices should be consistent with the definition of ''serious adverse event'' used by the international standard for clinical investigations of medical devices in human subjects (ISO 14155) [Ref. 88]. As we noted in our discussion of the term in the NPRM, the definition is consistent with established FDA standards, and we drew on the FDA definition of ''serious adverse event'' in 21 CFR 312.32(a) for IND applications in developing the definition because that FDA definition more fully characterizes the criteria for ''other serious problems'' as well as ''any life-threatening problem'' or ''[d]eath.'' In defining the term ''serious adverse event'' in its IND Safety Reporting regulations in 21 CFR 312.32(a), FDA considers an adverse event to be ''serious'' when, in the view of either the sponsor or the investigator, it ''results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate

medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.'' The other points we made in the NPRM are also relevant, and we reiterate them here to explain why we are not adopting the commenters' suggestion. A ''serious adverse event,'' as defined in 21 CFR 312.32(a), applies only in the context of drugs (including biological products). No fully equivalent term is defined in FDA regulations for medical devices. In 21 CFR 812.3(s), FDA defines an ''unanticipated adverse device effect'' as, in part, ''any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device'' that ''was not previously identified . . . in the investigational plan or application . . . or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.'' However, we did not consider this definition to be sufficient to meet the statutory requirement in section 402(j)(3)(I)(iii) of the PHS Act for submission of serious adverse event information that encompasses both anticipated and unanticipated events because it is restricted to unanticipated effects.

After considering the comments, we maintain the NPRM definition of ''serious adverse event'' in § 11.10(a) to mean ''an adverse event that results in any of the following outcomes: Death, a life-threatening adverse event as defined in 21 CFR 312.32, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the human subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of a substance use disorder.'' Although we adopted terms from an FDA drug regulation, we emphasize that ''serious adverse event,'' as defined for the purposes of this part, applies to both drugs and devices. Further, and as explained more fully in section IV.C.4. of this preamble, the rule does not require investigators or responsible parties to collect information that is not specified in the clinical trial protocol.

We use the phrase ''a substance use disorder'' instead of the phrase ''drug dependency or drug abuse,'' which is used in the FDA definition, for consistency with the latest version (fifth edition) of the Diagnostic and Statistical Manual of Mental Disorders [Ref. 89]. By referring to adverse events (and thus the definition of that term in this part), our definition of ''serious adverse event'' is broader than the FDA definition of ''serious adverse event'' in 21 CFR 312.32(a) because it encompasses any untoward or unfavorable medical occurrences associated with any intervention included in a clinical trial (not just the use of the FDA-regulated product), including any intervention(s) in any arm of the clinical trial that does not involve FDA-regulated products. In addition, as with our definition of ''adverse event,'' our definition of ''serious adverse event'' encompasses both anticipated and unanticipated effects regardless of attribution or association with the intervention.

Sponsor

In the NPRM, we defined ''sponsor'' in § 11.10(a) to mean ''either a 'sponsor' or 'sponsor-investigator,' as each is defined 21 CFR 50.3 or any successor regulation.'' As we explained, ''[s]ponsor'' is a term used in section 402(j) of the PHS Act to define responsible party (79 FR 69608). Section 402(j)(1)(A)(ix)(I) of the PHS Act explicitly defines ''sponsor'' as such term is defined at 21 CFR 50.3 or any successor regulation. Two types of sponsors are defined in 21 CFR 50.3, both of which, we noted, meet the definition of ''sponsor'' for the purposes of this part. The first type is a ''sponsor,'' defined in 21 CFR 50.3 as ''a person who initiates a clinical investigation but who does not actually conduct the investigation, *i.e.,* the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (*e.g.,* corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.'' The second type is a ''sponsor-investigator,'' defined in 21 CFR 50.3 as ''an individual who both initiates and actually conducts, alone or with others, a clinical investigation, *i.e.,* under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, *e.g.,* corporation or agency.'' As we noted, we believe that the definition of ''sponsor'' used in this part must encompass both a sponsor and a sponsor-investigator because both terms are relevant in determining who initiates the clinical trial.

We did not receive any comments on this definition, and we maintain it in the final rule to mean ''either a 'sponsor' or 'sponsor-investigator', as each is defined 21 CFR 50.3.'' Procedures for determining which individual or entity would be considered the sponsor of an applicable clinical trial or other clinical trial subject to this part are specified in § 11.4(c) and described in Section IV.A.2 of this preamble. As those sections explain, the individual or entity that is the sponsor is considered to be the responsible party of an applicable clinical trial or other clinical trial, unless and until that responsibility is delegated to the principal investigator, consistent with the requirements of section 402(j)(1)(A)(ix) of the PHS Act and this part.

Study Completion Date

The NPRM did not use the term ''study completion date'' or propose either a definition of it in § 11.10(a) or a data element for it in § 11.28, but we are including the term and data element in this final rule. We define the term ''study completion date'' in § 11.10(a) to mean ''for a clinical trial, the date the final subject was examined or received an intervention for purposes of final collection of data for the primary and secondary outcome measures and adverse events (*e.g.,* last subject's last visit), whether the clinical trial concluded according to the pre-specified protocol or was terminated.'' Section 402(j)(2)(A)(ii) of the PHS Act specifies the clinical trial registration information that must be submitted, although study completion date is not included. However, section 402(j)(2)(A)(iii) of the PHS Act permits the Secretary to ''modify the requirements for clinical trial [registration] information'' by regulation, provided that ''such a modification improves and does not reduce such clinical trial information.''

As discussed in Section IV.B.4, we believe that the study completion date is helpful in indicating when all primary and secondary outcome measures and the collection of all adverse event information, as specified in the protocol, will be completed and when final data collection has occurred. Therefore, we believe that requiring the submission of the study completion date improves and does not reduce clinical trial information.

Section 11.64(a)(3) describes when a responsible party's obligation to submit updates ends. Our definition of ''study completion date'' identifies the final date of data collection for the study, including for any primary and secondary outcomes and for adverse events. For adverse events, the last date of data collection is the end of the adverse event collection period specified by the protocol. The study completion date will be the end of this adverse event collection period if this period ends later than the last subject's last visit for the primary and secondary outcomes. As discussed in other sections of this preamble, the study completion date is relevant in determining the obligations for responsible parties to submit registration and results information. As described in Section IV.C.3 for partial results information deadlines under § 11.44(d), clinical trial results information specified in § 11.48 must be submitted no later than one year after the study completion date. In addition, the Study Completion Date,'' which is a registration data element, will be displayed on the posted record.

Although we did not receive any specific comments about adding a Study Completion Date data element, commenters did request that a mechanism be included in the PRS to make clear to responsible parties when they have fulfilled all obligations to update the study record, and when no further updates are required. A responsible party can use the ''study completion date'' definition and related data element in determining various obligations under this part, such as the deadlines for submitting partial results information under § 11.44(d). The ''study completion date'' is distinct from ''completion date,'' which, as discussed above, we refer to as the ''primary completion date.''

U.S. FDA-Regulated Device Product

In the NPRM, we defined ''FDA-regulated device'' in § 11.10(a) to mean ''for purposes of this part, a device subject to section 510(k), 515, 520(m), or 522 of the Federal Food, Drug, and Cosmetic Act.'' As we explained, this term and its definition are based on section 402(j)(1)(A)(ii) of the PHS Act, which defines ''applicable device clinical trial'' as including studies of a ''device subject to section 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act.'' We did not receive any comments on this definition and maintain it in § 11.10(a) of the final rule. However, because ''FDA'' is a term used by similar regulatory agencies in other countries, we have changed the term ''FDA-regulated device'' to ''U.S. FDA-regulated device product'' for clarity. As we have elsewhere, we now also use the term ''device product.'' A responsible party must submit information, in accordance with § 11.28, about whether the trial ''studies a U.S. FDA-regulated device product.'' We explain further whether a trial studies a U.S. FDA-regulated device product in Section IV.B.2 of this preamble in our elaboration on the meaning of an ''applicable device clinical trial.'' We also include the applicable U.S.C. statutory citations in the definition.

U.S. FDA-Regulated Drug Product

In the NPRM, we defined ''FDA-regulated drug'' in § 11.10(a) to mean ''for purposes of this part, a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or a biological product subject to section 351 of the Public Health Service Act.'' As we explained, this term and its definition are based on section 402(j)(1)(A)(iii) of the PHS Act, which defines ''applicable drug clinical trial'' as including studies of a ''drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to section 351 of the [Public Health Service Act].'' We did not receive any comments on this definition and maintain it in § 11.10(a) of the final rule. However, because ''FDA'' is a term used by similar regulatory agencies in other countries, we have changed the term ''FDA-regulated drug'' to ''U.S. FDA-regulated drug product'' for further clarity. Additionally, for clarity, we now use the term ''drug product'' rather than ''drug.'' A responsible party must submit information in accordance with § 11.28 about whether the trial ''studies a U.S. FDA-regulated drug product.'' We explain further whether a trial studies a U.S. FDA-regulated drug product in Section IV.B.2 of this preamble in our elaboration on the meaning of an ''applicable drug clinical trial''. We also include the applicable U.S.C. statutory citations in the definition.

Section 11.10(b) defines certain data elements that are part of the clinical trial registration information that must be submitted to *ClinicalTrials.gov* under this part. The data elements defined in § 11.10(b) are enumerated in § 11.28(a).

B. Subpart B—Registration

1. 11.20—Who must submit clinical trial registration information?

Overview of Proposal

Proposed § 11.20 required that ''[t]he responsible party for an applicable clinical trial specified in § 11.22 must register the applicable clinical trial by submitting clinical trial registration information specified in § 11.28 for that clinical trial.'' As we explained in the NPRM, this approach is consistent with section 402(j)(2)(C) of the PHS Act, which states that the ''responsible party for an applicable clinical trial . . . shall submit to the Director of NIH for inclusion in the registry data bank the [clinical trial registration information]'' (79 FR 69609).

Comments and Response

There were no comments received on this section.

Final Rule

The final rule maintains § 11.20 as proposed, except clarifies the wording for consistency with § 11.40. Section 11.20 requires that ''[t]he responsible party for an applicable clinical trial specified in § 11.22 must submit clinical trial registration information for that clinical trial.''

2. 11.22—Which applicable clinical trials must be registered?

Overview of Proposal

In proposed § 11.22(a), the Agency interpreted section 402(j)(2)(C) of the PHS Act to specify which applicable clinical trials must be registered with *ClinicalTrials.gov*. As we explained in the NPRM, proposed § 11.22(b) set forth an approach for determining whether or not a clinical trial meets the statutory definitions of an applicable device clinical trial and an applicable drug clinical trial, as established in section 402(j)(1) of the PHS Act (79 FR 69610). The proposed approach used a series of specific registration data elements and corresponding criteria to determine whether a clinical trial or study meets the definition of an applicable clinical trial (*i.e.,* Study Type of the trial is ''interventional,'' Study Phase is other than ''Phase 1,'' etc.). We also pointed out that ''algorithms'' following the approach outlined in the regulations would also be made available outside the registration process (*e.g.,* online at *http://prsinfo.clinicaltrials.gov/fdaaa.html*), and study sponsors could use such algorithms to evaluate whether a particular trial meets the definition of

applicable clinical trial (79 FR 69610). The NPRM invited public comment on the approach proposed in § 11.22(b) for determining whether a clinical trial or study is an applicable clinical trial. It also requested comments on whether there are any types of applicable clinical trials that would be misidentified by this approach.

Comments and Response

Commenters addressed the NPRM's approach for facilitating the determination of which clinical trials or studies are applicable clinical trials that must be registered with *ClinicalTrials.gov*. Several commenters supported the proposed approach for determining whether a study is an applicable clinical trial, with a few commenters suggesting that the rationale and approach would likely reduce administrative burden for stakeholders. One suggested that the data elements required for the determination process be made available to sponsors outside of the registration process and that *ClinicalTrials.gov* issue dated receipts to provide an audit trail detailing whether or not a clinical trial was determined to be an applicable clinical trial. In order to assist users in evaluating, prior to beginning the registration process, whether their clinical trial or study is an applicable clinical trial and potentially subject to the requirements of the statute and the final rule, a checklist-based tool will be made available at *https://prsinfo.clinicaltrials.gov* (or successor site) for sponsors and others before the effective date of the rule. Although proposed § 11.22(b) included the criteria for determining whether a trial is an applicable clinical trial, the checklist tool is external to the *ClinicalTrials.gov* PRS and separate from the registration process. The outcome generated by the checklist tool will not be retained by the Agency and will not be binding on either the user or any government Agency in any future actions. While the tool is intended to be useful, it is not intended to be determinative of the applicability of the statute or this rule. Thus, we do not agree that a dated receipt for the outcome is necessary.

A few commenters opposed the overall proposed approach. One stated that it would be neither helpful nor appropriate and requested that study sponsors be allowed to make the determination rather than respond to each specific element. As noted, the Agency is not making the checklist tool available within the internal PRS system. The proposed approach provides responsible parties or other users with a method to help evaluate whether a particular clinical trial is an applicable clinical trial prior to data submission. Since 2009, a draft Elaboration of Definitions, which expounds on the definition of applicable clinical trial [Ref. 90], and *ClinicalTrials.gov* registration data elements have been available to allow sponsors to indicate whether a clinical trial or study is an applicable clinical trial (*i.e.,* ''Section 801 Clinical Trial'') [Ref. 85]. However, based on requests for clarification we have received to date, some users have found application of these definitions and data elements difficult to implement in practice. Building on our experience in responding to such requests and the comments received, breaking the definition of applicable clinical trial into components that can be explained in terms of objective data elements has often facilitated understanding of the applicable clinical trial definition and the user's evaluation process for their particular clinical trial or study. Other than comments on the interpretation of the definition of applicable clinical trial and its components (*e.g.,* definition of ''controlled,'' application to studies of ''combination products''), which are discussed elsewhere in the preamble (see Section IV.A.5), we did not receive any specific examples, as invited, of situations in which the proposed approach would misidentify an applicable clinical trial. However, as addressed below, other commenters offered suggestions or raised questions about our proposal.

Some commenters observed that the data elements used for the Applicable Clinical Trial assessment checklist were either too broadly or too poorly defined. One commenter suggested that additional data elements be added to determine whether a study is interventional. We clarify or provide elaboration on the definitions (see § 11.10) for a number of data elements, such as ''interventional,'' used to determine whether a study is an applicable clinical trial. In addition, we are committed to providing additional guidance as needed when new issues with interpretation are raised. The Agency believes that this data element-based approach provides an objective, transparent set of criteria for responsible parties and other users to evaluate, prior to registering a trial, whether a clinical trial or study is an applicable clinical trial and for such users of *ClinicalTrials.gov* to understand the data elements used in evaluating whether a clinical trial or study is an applicable clinical trial. Prior to registration a sponsor or other user will be able to use the external checklist tool, which will be based on the set of data elements identified in § 11.22(b), to assess whether a clinical trial or study is considered an applicable clinical trial. Once clinical trial registration information has been submitted, the Agency will be able to identify applicable clinical trials based on the set of data elements identified in § 11.22(b). Public users of *ClinicalTrials.gov*, other than responsible parties, should be able to understand whether a registered trial is an applicable clinical trial. Although we have not conducted a formal pilot study, as suggested by a commenter, the approach is responsive to the challenges users have experienced in the past while trying to determine whether their clinical trial or study meets the definition of applicable clinical trial.

Commenters requested that the Agency provide examples of clinical trials that do not fulfill the proposed criteria for applicable clinical trials, and a couple of commenters observed that case studies would be helpful for clarification purposes. The Agency intends to continue making explanatory documents and other materials available, including examples, case studies, and a publicly-accessible checklist-based tool (described above) consisting of the relevant data elements and detailed explanation of each criterion at *https://prsinfo.clinicaltrials.gov* (or successor stite). Finally, the Agency believes that it has identified the minimum set of criteria (corresponding to the registration data elements) needed to identify applicable clinical trials, which should minimize burden on the responsible parties.

Several commenters recommended that the Agency provide responsible parties with a mechanism to explain why a clinical trial is not an applicable clinical trial and/or to appeal the outcome of the proposed approach. However, although we specifically asked in the NPRM for examples of cases in which the approach outlined in the NPRM and discussed above would lead to a misclassification of a clinical trial (*i.e.,* either by inappropriately including a trial that is not an applicable clinical trial or excluding a trial that is), no examples were submitted. Further, as mentioned previously, the checklist will be available as a tool separate from the *ClinicalTrials.gov* registration process in the PRS. By having each criterion correspond to one or more standard data elements, the evaluation and assessment process follows a checklist approach based on factual information (*e.g.,*

whether or not the Study Type is ''interventional'' as defined; whether a drug is regulated by the U.S. FDA under section 505 of the FD&C Act or section 351 of the PHS Act). Responsible parties or other users who use the checklist tool are responsible for using accurate data about a clinical trial or study and for conducting the evaluation. Since the outcome is dependent on the factual data relied on by a responsible party or other user, and the outcome of the assessment will not be binding on either the user or any government Agency in any future actions, we do not see a need for a mechanism for responsible parties or other users to comment on a particular outcome of the external checklist tool or an appeal process to dispute the outcome. The Agency will provide contact information for obtaining assistance with questions that arise about the interpretation of a criterion or a relevant data element definition for which answers cannot be found in Agency documents or other existing materials.

Another commenter requested that the *ClinicalTrials.gov* Web site remove the ''late'' status and ''problems'' designation for trials that do not meet the definition of ''applicable clinical trial'' under the regulation. It is our understanding that this comment refers to an online tool that is currently available to help responsible parties manage their study records when using the PRS. Since all of the data elements needed to evaluate whether a clinical trial or study is an applicable clinical trial are not yet available, the current online tool only approximates which submissions may be ''late'' and which trials are ''*probable* applicable clinical trials.'' The Agency used the term ''probable applicable clinical trials'' (pACTs) to refer to the estimated number of clinical trials subject to section 402(j) of the PHS Act prior to the effective date of the rule. This approach relied on the set of clinical trial registration data elements available prior to enactment of the final rule, but did not include all of the data elements necessary to determine which studies are applicable clinical trials as specified in § 11.22(b) of the final rule. The pACTs were defined as records listing an ''interventional'' Study Type; with at least one Intervention Type as ''Biological,'' ''Drug,'' ''Device,'' ''Genetic,'' or ''Radiation;'' a Study Phase other than ''Phase 0'' or ''Phase 1;'' a Primary Completion Date on or after January 2008 or, if the Primary Completion Date was missing, a Study Completion Date on or after January 2008, or any record for which both the Primary Completion Date and the Study Completion Date are missing; an Overall Recruitment Status other than ''Withdrawn,'' and at least one Facility Location Country in the ''United States'' or if none, indication that the study is conducted under an FDA IND or IDE.

Promulgation of the final rule and implementation of several new data elements (*e.g.,* Studies an FDA-regulated Drug [or Device]), enables the Agency to be better able to identify applicable clinical trials more accurately in the PRS and on the public Web site. In addition, it enables the Agency to create other tools within the PRS to assist responsible parties with managing their responsibilities. Misidentified trials, as referred to in the comments, should be able to be addressed.

Final Rule

Taking into consideration the submitted comments, as well as the statutory definitions of the terms, ''applicable device clinical trial'' and ''applicable drug clinical trial,'' the rule retains the proposed scope for required registration of applicable clinical trials, but modifies the approach for evaluating whether a study is an applicable clinical trial as specified in § 11.22(b) based on the Agency's revised interpretation of ''control or controlled,'' as described elsewhere in the preamble (Section IV.A.5). Additionally, the final rule clarifies that ''device'' means ''device product'' and ''drug'' means ''drug product.'' The final rule also clarifies that the approach in § 11.22(b) for evaluating whether a study is an applicable clinical trial applies to trials initiated on or after the effective date of the final rule.

Section 11.22(a)(1) and (2) state that registration is required for: (1) ''[a]ny applicable clinical trial that is initiated after September 27, 2007;'' and (2) ''[a]ny applicable clinical trial that is initiated on or before September 27, 2007 and is ongoing on December 26, 2007 [. . .].'' Section 11.22(a)(3) provides clarification for determining the date on which an applicable clinical trial is initiated, stating that ''[a]n applicable clinical trial, other than a pediatric postmarket surveillance of a device product that is not a clinical trial, is considered to be initiated on the date on which the first human subject is enrolled.''

Based on the Agency's interpretation of the term ''applicable device clinical trial'' as defined in section 402(j)(1) of the PHS Act, § 11.22(b)(1) states that a clinical trial is considered an applicable device clinical trial if (1) it is a pediatric postmarket surveillance of a device product required by FDA under section 522 of the FD&C Act (regardless of whether the pediatric postmarket surveillance is a clinical trial), or (2) it is a clinical trial with one or more arms that meets all of the following criteria: (a) The Study Type is interventional; (b) the Primary Purpose selected is any other than feasibility; (c) the clinical trial Studies a U.S. FDA-regulated Device; and, (d) one or more of the following applies: At least one Facility Location is within the U.S. or one of its territories, the device under investigation is a Product Manufactured in and Exported from the U.S. or one of its territories for study in another country, or the clinical trial has a U.S. Food and Drug Administration IDE Number. We also note that the final rule does not include the proposed criterion regarding the Number of Arms and Single Arm Controlled data elements in § 11.22(b)(1)(ii)(C) and (b)(2)(iii) of the NPRM because the Agency considers all clinical trials with one or more arms and pre-specified primary or secondary outcome measures controlled for purposes of the final rule (see discussion of ''control or controlled'' in Section IV.A.5 of this preamble).

Based on the Agency's interpretation of the term ''applicable drug clinical trial'' as defined in section 402(j)(1) of the PHS Act, § 11.22(b)(2) states that a clinical trial with one or more arms is considered an applicable drug clinical trial if it meets all of the following: (1) The Study Type is interventional; (2) the Study Phase is other than phase 1; (3) the clinical trial Studies a U.S. FDA-regulated Drug Product; and, (4) one or more of the following applies: At least one Facility Location is within the U.S. or one of its territories, the drug product under investigation is a Product Manufactured in and Exported from the U.S. for study in another country, or the clinical trial has a U.S. Food and Drug Administration IND Number.

With respect to Study Phase and the determination process, we do not consider a phase 1/phase 2 trial (*i.e.,* a trial with characteristics of both phase 1 and phase 2 studies trials) to be a phase 1 trial. If a clinical trial is initially registered as phase 1/phase 2 trial, it is considered to be a phase 2 trial. If the trial subsequently proceeds through only the phase 1 stage and/or is terminated before reaching phase 2, the Study Phase data element may be updated to indicate that the trial is a phase 1 trial, in which case it would not be considered an applicable drug clinical trial and would not be subject to the requirements for results information submission specified in subpart C. However, submitted registration information would continue

to be posted in the *ClinicalTrials.gov* data bank.

While most applicable clinical trials will meet the definition of either an applicable device clinical trial or an applicable drug clinical trial, some applicable clinical trials that study multiple intervention types (*e.g.,* in different arms of the clinical trial) could meet both definitions. For example, a clinical trial with facility locations in the U.S. that studies a U.S. FDA-regulated drug product in one arm, studies a U.S FDA-regulated device product in another arm, and compares outcomes of the two arms would meet both definitions. If the U.S. FDA-regulated device product studied in such an applicable clinical trial is not approved or cleared by FDA for any use, we will not post clinical trial registration information for that applicable clinical trial prior to the date of approval or clearance of the device product, consistent with § 11.35(b)(2)(i), unless the responsible party indicates, pursuant to § 11.35(b)(2)(ii), that it authorizes such posting.

3. 11.24—When must clinical trial registration information be submitted?

Overview of Proposal

Proposed § 11.24 specified the deadlines by which a responsible party must submit clinical trial registration information for an applicable clinical trial to *ClinicalTrials.gov*, implementing section 402(j)(2)(c) of the PHS Act. As explained in the NPRM, proposed § 11.24(a) specified the general registration deadline requiring submission by the later of December 26, 2007, or 21 calendar days after enrollment of the first human subject in a clinical trial, as specified in section 402(j)(2)(C)(i) and (ii) (79 FR 69611). Proposed § 11.24(b) implemented two exceptions: (1) For applicable clinical trials that are not for a serious or life-threatening disease or condition and that were initiated on or before enactment of FDAAA, the registration deadline is not later than September 27, 2008, or 21 calendar days after the first human subject is enrolled, whichever date is later, consistent with section 402(j)(2)(C)(iii) of the PHS Act, and (2) for a pediatric postmarket surveillance of a device product that is not a clinical trial, which is defined as an applicable device clinical trial in section 402(j)(1)(A)(ii)(II) of the PHS Act, the registration deadline is not later than December 26, 2007, or 21 calendar days after FDA approves the postmarket surveillance plan, whichever date is later (79 FR 69611).

Comments and Response

Commenters addressed the registration submission deadlines in proposed § 11.24. The commenters suggested that the final rule require general registration prior to enrollment of the first human subject, rather than allow up to an additional 21 calendar days as proposed. One commenter noted that such a deadline would be consistent with requirements specified in the EU Clinical Trials Regulation as well as the Declaration of Helsinki. Another commenter also requested that the final rule omit the exception to the general deadline for registering applicable clinical trials not for a serious or life-threatening disease or condition specified in proposed § 11.24(b)(1). The Agency is not revising proposed § 11.24 as suggestedby the comments. Section 11.24 accurately reflects the statutory requirements for submission of registration information.

Final Rule

Taking into consideration the commenters' suggestions and the statutory requirements for registration information submission deadlines, the final rule maintains the approach proposed in § 11.24(a) and (b) except that it clarifies that ''device'' means ''device product.'' In addition, we have clarify that the clinical trial registration information that must be submitted will either be the information specified in section 402(j)(2)(A)(ii) of the PHS Act or in § 11.28(a). Consistent with the discussion in section IV.F., the requirements for applicable clinical trials will differ based on the initiation date of the applicable clinical trial. Final § 11.24(a) generally requires a responsible party to submit clinical trial registration information 21 calendar days after the first human subject is enrolled in the clinical trial. Final § 11.24 also provides exceptions to this general registration submission deadline for applicable clinical trials that are clinical trials and were (1) initiated on or before September 27, 2007, and (2) ongoing as of December 26, 2007. For applicable clinical trials for a serious or life-threatening disease or condition, responsible parties were required to submit registration information by December 26, 2007, under § 11.24(a). Examples of serious or life-threatening diseases or conditions include acquired immunodeficiency syndrome, all other stages of human immunodeficiency virus (HIV), Alzheimer's disease, cancer, or heart failure [Ref. 78, 79]. For applicable clinical trials not for a serious or life-threatening disease or condition, responsible parties were required to submit registration information by September 27, 2008, under § 11.24(b)(1).

4. § 11.28—What constitutes clinical trial registration information?

§ 11.28—Overall

Overview of Proposal

Proposed § 11.28 identified the structured information, or data elements, that constitute clinical trial information that a responsible party must submit in order to register an applicable clinical trial. Section 402(j)(2)(A)(ii) of the PHS Act specifies a number of data elements that must be submitted to *ClinicalTrials.gov* for registration. In general, the proposed data elements in § 11.28 conformed to the items enumerated in section 402(j)(2)(A)(ii) of the PHS Act. In many instances, the Agency, through the proposed rulemaking, had restated or clarified the registration data elements required by section 402(j)(2)(A)(ii) of the PHS Act. In addition, section 402(j)(2)(A)(iii) of the PHS Act expressly authorizes the Secretary to modify the registration data elements, by regulation, if a rationale is provided as to why such a modification ''improves and does not reduce'' such information. In developing the proposed set of data elements for registration, we carefully considered the items enumerated in section 402(j)(2)(A)(ii) of the PHS Act, the mandate in section 402(j)(2)(A)(i) to ''expand'' the existing registration data bank, and the intent to expand the data bank ''to enhance patient enrollment and provide a mechanism to track subsequent progress of clinical trials'' (see section 402(j)(2)(A)(i) of the PHS Act). We also took into consideration the WHO Trial Registration Data Set and have sought to maintain consistency with the clinical trial registration requirements of ICMJE [Ref. 73, 2].

As we noted in the NPRM, careful consideration was given to the data elements that were part of the data bank prior to passage in 2007 of section 402(j) of the PHS Act, some of which are not expressly required under section 402(j)(2)(A)(ii) of the PHS Act, but which we considered necessary to fulfill both the purpose of the expansion of registration information contained in *ClinicalTrials.gov* and certain other requirements of section 402(j) of the PHS Act. We later consulted with a wide range of groups, including the NLM Board of Directors Working Group on Clinical Trials, internal NIH and joint NIH–FDA working groups and committees, the FDA Risk Communication Advisory Committee, the HHS Secretary's Advisory

Committee on Human Research Protections, the Drug Information Association Clinical Trial Disclosure Special Interest Area Community, and a Clinical and Translational Science Awards *ClinicalTrials.gov* Task Force [Ref. 72, 91, 91]. We believe, in general, that maintaining consistency with the pre-existing *ClinicalTrials.gov* data elements is consistent with the intent of section 402(j) of the PHS Act. Not only do we presume that Congress was familiar with those existing definitions when it developed and passed section 402(j) of the PHS Act, we also believe that maintaining consistency achieves several important goals. It is intended to minimize confusion for those who submitted registration information to *ClinicalTrials.gov* prior to enactment of section 402(j) of the PHS Act as well as minimize the level of effort required by those who previously established automated computer-based processes for submitting and updating registration data in *ClinicalTrials.gov*, rather than entering the data manually into the data bank. We believe that maintaining consistency serves the public by facilitating cross-comparison of entries made before and after enactment of section 402(j) of the PHS Act and that it also ensures that the proposed clinical trial registration information requirements would not have the effect of reducing the amount of information available for newly registered clinical trials as compared to those registered prior to the passage in 2007 of section 402(j) of the PHS Act, a result that we believe would be contrary to the intent of section 402(j) of the PHS Act. For these reasons, we believe that requiring the submission of data elements that were expected to be submitted to *ClinicalTrials.gov* prior to the passage in 2007 of section 402(j) of the PHS Act in order to register a clinical trial improves and does not reduce the clinical trial information submitted to *ClinicalTrials.gov*.

While developing our proposed set of data elements for clinical trial registration information for the NPRM, we decided to exercise our authority under section 402(j)(2)(A)(iii) of the PHS Act to modify the section 402(j)(2)(A)(ii) requirements for registration information in order to achieve the following objectives:

(1) Specify a particular structure for submitting certain clinical trial registration information in order to (a) help the public use the data bank more easily and be able to compare entries, consistent with section 402(j)(2)(B)(iv) of the PHS Act; (b) enable searching of the data bank using criteria listed in sections 402(j)(2)(B)(i) and (ii) of the PHS Act; and (c) facilitate the submission of complete and accurate information by responsible parties.

(2) Enable effective implementation of, or compliance with, other provisions of section 402(j) of the PHS Act and this part, *e.g.,* proposed adding data elements to indicate whether a product under study in a clinical trial is manufactured in the United States and whether a study is a pediatric postmarket surveillance of a device product, both of which are important to help determine whether a study meets the definition of an applicable clinical trial.

(3) Improve the quality and consistency of clinical trial registration information, *e.g.,* proposed adding the Other Intervention Name(s) and Intervention Description data elements to help users identify and differentiate among similar interventions studied in registered clinical trials.

(4) Demonstrate whether clinical trials registered in the data bank have complied with ethical and scientific review procedures in accordance with applicable statutes and regulations, *e.g.,* proposed adding the Human Subjects Protection Review Board Status data element to indicate to potential human subjects and other users whether an applicable clinical trial has received needed approvals or is not subject to such requirements (79 FR 69611).

Several commenters supported the additional registration data elements proposed in the NPRM. An additional commenter requested that the final rule minimize the number of required registration data elements to provide more flexibility for the reporting of different types of trials. In developing the proposed registration data elements, the Agency carefully considered the statutory provisions and additional requirements in order to carry out those mandates. We believe that the data elements proposed in the NPRM represent a ''minimum'' data set of the information required to describe and understand key information about a clinical trial. Nevertheless, we have modified some of the proposed definitions and requirements for particular data elements in the final rule in response to public comments as well as on our own initiative (*e.g.,* for clarity or consistency).

§ 11.28(a)—Clinical Trial

Overview of Proposal

Proposed § 11.28(a) specified the data elements that a responsible party would be required to submit to *ClinicalTrials.gov* to register an applicable clinical trial other than a pediatric postmarket surveillance of a device that is not a clinical trial. As we described in the NPRM, the clinical trial registration information data elements are grouped into the four categories used in section 402(j)(2)(A)(ii) of the PHS Act: (1) Descriptive information, (2) recruitment information, (3) location and contact information, and, (4) administrative data. Additional data elements that the Agency proposed were listed in the categories in which they best fit. The proposed clinical trial registration information data elements, grouped by category, were described in detail in the NPRM. See Section IV.B.4(a) of the NPRM for details about the data elements under proposed § 11.28(a) (79 FR 69612).

For each data element defined in proposed § 11.28(a), we describe the following: (1) The proposed definition, (2) any specific public comment(s) we received about the data element and our response(s), and (3) the definition used in § 11.28(a) of the final rule. The information about each data element is ordered by section number as assigned in the codified section of the final rule, which also parallels section 402(j)(2)(A)(ii) of the PHS Act. We note that in the final rule some of the names of the data elements, as well as their numbers, differ from those assigned in the NPRM because of modifications to the data elements, all of which are described in the context of each specific data element. After discussing the last registration data element listed under § 11.28(a) of the final rule (*i.e.,* Responsible Party Contact Information in § 11.28(a)(2)(iv)(F)), we address data elements that were suggested in the public comments but were not added in the final rule.

We have made one overall change to the structure of § 11.28(a) and (b). In light of our determination that the registration requirements that apply to an applicable clinical trial are determined by the date on which the trial is initiated, *i.e.,* the actual Study Start Date, as defined in § 11.10(b)(16) (see discussion below in section IV.F.), we have indicated in both § 11.28(a) and (b) that for applicable clinical trials that must be registered with *ClinicalTrials.gov* as specified in section 402(j)(2)(C) of the PHS Act or § 11.22, the responsible party must submit the information specified in section 402(j)(2)(A)(ii) of the PHS Act or the data elements listed in § 11.28, as applicable.

Based on this modification, § 11.28(a)(1) requires that ''[f]or such applicable clinical trials that were initiated before January 18, 2017, the responsible party must submit the

information specified in section 402(j)(2)(A)(ii) of the Public Health Service Act (42 U.S.C. 282(j)(2)(A)(ii)).'' Section 11.28(a)(2) requires the data elements described below for such applicable clinical trials that are initiated on or after January 18, 2017.

(i) Descriptive Information

(A) *Brief Title.* In § 11.10(b)(1) of the NPRM, Brief Title was defined as ''a short title of the clinical trial written in language intended for the lay public, including any acronym or abbreviation used publicly to identify the clinical trial.'' Section 402(j)(2)(A)(ii)(I)(aa) of the PHS Act specifically requires the submission of a brief title as part of the clinical trial information submitted at registration, but it does not define the term, other than to indicate that the title is ''intended for the lay public.'' As explained in the NPRM, we interpreted this requirement to mean that potential human subjects should be able to understand, from the brief title, the general purpose of the clinical trial and distinguish it from others listed in the data bank. Additionally, based on our experience to date with *ClinicalTrials.gov*, we recognized that acronyms are frequently used to refer to clinical trials (*e.g.,* ''ACCORD'' for the Action to Control Cardiovascular Risk in Diabetes trial or ''STAR*D'' for the Sequenced Treatment Alternatives to Relieve Depression trial), and we believe that it is important for such acronyms to be included in the registry to enable users of the data bank to identify clinical trials that they may see referenced in other media (*e.g.,* news reports, journal articles). As such, we considered an acronym used to identify a clinical trial to be part of the brief title (79 FR 69612). We received no comments on this description and therefore maintain the proposed description in the final rule. We note that a Brief Title intended for the lay public should include, where possible, information on the participants, condition being evaluated, and intervention(s) studied.

(B) *Official Title.* In § 11.10(b)(2) of the NPRM, we defined Official Title as ''[t]he title of the clinical trial, corresponding to the title of the protocol.'' As described in the NPRM, while not explicitly required in section 402(j)(2)(A)(ii)(I) of the PHS Act, we used the authority in section 402(j)(2)(A)(iii) of the PHS Act to propose to require a responsible party to submit an official title as part of clinical trial information when registering an applicable clinical trial on *ClinicalTrials.gov*. We expressed our belief that the Official Title will complement the Brief Title that is intended for the lay public by providing a technical title that will help researchers understand the general purpose of the study. The official title would also be helpful in associating the clinical trial on *ClinicalTrials.gov* with information about the clinical trial contained in other sources, such as scientific publications, regulatory submissions, and media reports, which often use the official title of the study protocol (79 FR 69612). We received no comments on this description and therefore maintain the proposed description in the final rule. We note that Official Title is also consistent with the WHO Trial Registration Data Set (version 1.2.1) (WHO data item #10) and ICMJE registration policies, which require the submission of a ''scientific title'' [Ref. 73, 2].

(C) *Brief Summary.* In § 11.10(b)(3) of the NPRM, Brief Summary was described as ''a short description of the clinical trial, including a brief statement of the clinical trial's hypothesis, written in language intended for the lay public.'' As noted in the NPRM, section 402(j)(2)(A)(ii)(I)(bb) of the PHS Act expressly requires a ''brief summary'' to be submitted as clinical trial registration information, but it does not define the term other than to indicate that the brief summary is ''intended for the lay public'' (79 FR 69612). We received no comments on this description and therefore maintain the proposed description in the final rule.

(D) *Primary Purpose.* Under § 11.10(b)(4) of the NPRM, Primary Purpose referred to ''the main objective of the intervention(s) being evaluated by the clinical trial.'' We noted in the NPRM that section 402(j)(2)(A)(ii)(I)(cc) of the PHS Act expressly requires the ''primary purpose'' of the intervention(s) to be submitted as clinical trial registration information, but it does not define the term (79 FR 69612). We received no comments on this description and maintain the proposed definition in the final rule.

In the NPRM, we stated that we would require a responsible party to provide a response selected from the following set of options: ''Treatment,'' ''prevention,'' ''diagnostic,'' ''supportive care,'' ''screening,'' ''health services research,'' ''basic science,'' ''feasibility,'' or ''other'' (79 FR 69612) We are modifying the name of one of these options, from ''feasibility'' to ''device feasibility.'' This change helps responsible parties more easily recognize that the option is intended to be limited to the type of feasibility study of a device that is described as being excluded from the definition of an applicable device clinical trial as specified in section 402(j)(1)(A)(ii) of the PHS Act and defined in § 11.10(a) of this part. ''Device feasibility'' is distinguished from the general term ''feasibility,'' which is sometimes used in research to describe a study that is performed to determine the practicality of conducting a full clinical trial. We also note that a responsible party may nevertheless voluntarily register a clinical trial that is a feasibility study of a device. Such registration would be a voluntary submission of clinical trial information under section 402(j)(4)(A) of the PHS Act and § 11.60 of the final rule.

In addition, we would like to provide additional clarification for responsible parties regarding the options available under Primary Purpose. These clarifications are as follows: ''Treatment'' should be selected when one or more interventions are being evaluated for treating a disease, syndrome, or condition; ''prevention'' should be selected when one or more interventions are being assessed for preventing the development of a specific disease or health condition; ''diagnostic'' should be selected when one or more interventions are being evaluated for identifying a disease or health condition; ''supportive care'' should be selected when one or more interventions are being evaluated for maximizing comfort, minimizing side effects, or mitigating against a decline in the subject's health or function; ''screening'' should be selected when one or more interventions are being assessed or examined for identifying a condition, or risk factors for a condition, in people who are not yet known to have the condition or risk factor; ''health services research'' should be selected when one or more interventions are being evaluated for the delivery, processes, management, organization or financing of health care; ''basic science'' should be selected when one or more interventions are being used for examining the basic mechanism of action (*e.g.,* physiology, biomechanics), of an intervention or disease process; ''device feasibility'' should be selected when a device product is being evaluated for the feasibility of the product or of a test prototype device and not health outcomes; and ''other'' should be selected when none of the other options apply.

(E) *Study Design.* Proposed § 11.10(b)(5) defined Study Design as ''a description of the manner in which the clinical trial will be conducted'' and required information about the following important aspects of a clinical

trial: Interventional study model, number of arms, arm information, allocation, masking, and whether a single-armed clinical trial is controlled. As we noted in the NPRM, this proposed definition of Study Design, including the key attributes, conforms to ICH Guidelines [Ref. 56] and is consistent with ''study type'' of the WHO Trial Registration Data Set (version 1.2.1) (WHO data item #15) and ICMJE registration policies [Ref. 2, 73]. Section 402(j)(2)(A)(ii)(I)(dd) of the PHS Act expressly requires ''study design'' to be submitted as part of clinical trial registration information, but it does not define the term. Because there are many important aspects of a study design, and information about each is relevant to ensuring that the descriptions of study designs are complete and comparable across clinical trials, we proposed to require that several components of study design be submitted, as described below. Although none of these terms is used in section 402(j) of the PHS Act, we pointed out that we believe that each is a key component of study design (79 FR 69613). We received no comments on the overall definition and therefore generally maintain the proposed definition of Study Design in the final rule, with one exception.

The final rule does not include the proposed Single Arm Controlled? data item of the Study Design data element, which was defined in § 11.10(b)(5)(vi) of the NPRM as ''[f]or a single-armed clinical trial only, whether or not the clinical trial is controlled, as specified by the protocol or statistical analysis plan.'' This data item of the Study Design data element was proposed in the NPRM to assist the Agency, responsible parties, and users of the data bank in determining whether a clinical trial with only one arm meets the definition of an applicable clinical trial because it includes a control or is controlled. However, as described in Section IV.A.5, the Agency has clarified its interpretation of ''control or controlled'' to make clear that all single-arm interventional studies or clinical trials with pre-specified primary or secondary outcome measures are considered to be ''controlled'' for purposes of this part. As such, the proposed Single Arm Controlled? component of the Study Design data element is not necessary and has been removed from §§ 11.10(b) and 11.22(b) of the final rule.

Interventional Study Model. In § 11.10(b)(5)(i) of the NPRM, this data item was defined as ''[t]he strategy for assigning interventions to human subjects.'' As stated in the NPRM, responsible parties would be required to select an entry from the following limited set of proposed options: ''single group'' (*i.e.,* clinical trials with a single arm), ''parallel'' (*i.e.,* participants are assigned to one of two or more groups in parallel for the duration of the study), ''cross-over'' (*i.e.,* participants receive one of two alternative interventions during the initial phase of the study and receive the other intervention during the second phase of the study), and ''factorial'' (*i.e.,* two or more interventions, each alone and in combination, are evaluated in parallel against a control group). No ''other'' option was proposed. To address situations in which a clinical trial might use a modified version of one of these models, or the responsible party might wish to provide more information about the specific implementation of the model, we proposed that responsible parties also be able to provide an optional additional free-text description containing more specific details about the interventional study model. We invited public comment on this proposed definition and approach (79 FR 69613). A few commenters recommended that the final rule add an ''other'' option for Interventional Study Model, with one commenter suggesting ''enrichment designs'' and ''adaptive borrowing of historical data'' as examples. We note that these examples do not appear to represent interventional study models that differ conceptually from those proposed in the NPRM. For example, even though ''enrichment designs'' involve prespecified study periods that allow researchers to select subsets of enrolled participants who are likely to be particularly sensitive to the studied intervention (*e.g.,* to demonstrate the effect of a drug), we believe that the underlying interventional study model involves at least one of the suggested options (*i.e.,* ''single-group,'' ''parallel,'' ''cross-over,'' or ''factorial''). The fact that a study involves an enrichment design could be noted in the proposed optional additional free-text description field. The final rule retains the name and definition of Interventional Study Model as proposed in the NPRM. In reviewing this proposed data item, however, we identified two modifications to the set of proposed options. First, based on our experience in operating *ClinicalTrials.gov*, we add the option of ''sequential'' as we believe that it represents an Interventional Study Model that is fundamentally different from the other options available for selection under Interventional Study Model and is fairly common among drug studies (*e.g.,* dose escalation). Thus, we have added ''sequential'' as an option under the Interventional Study Model data item; responsible parties would select this option to indicate that groups of participants are assigned to receive interventions based on prior milestones being reached in the study, such as in some dose escalation and adaptive design studies. Second, we have also modified the description of the ''cross-over'' option to clarify that this term refers to study designs in which participants are assigned to receive one of two (or more) alternative interventions during the initial phase of the study followed by the other intervention(s) during subsequent phase(s) of the study. This modification clarifies that cross-over studies are not restricted to just two interventions, but may involve two (or more) interventions [Ref. 84].

Number of Arms. In § 11.10(b)(5)(ii) of the NPRM, this data item was defined as ''[t]he number of arms in the clinical trial. For a trial with multiple periods or phases that have different numbers of arms, the maximum number of arms during any period or phase.'' We noted that the term ''arm'' was defined in proposed § 11.10(a) and that some clinical trials contain multiple periods or phases, each of which might use different numbers of arms. We also clarified in the NPRM that we do not consider historical controls to be an ''arm'' of a clinical trial for the purposes of this part, therefore, they would not be counted in the number of arms (79 FR 69613). One commenter suggested that, for reporting trials with ''mutually reporting arms,'' the maximum number of arms listed should be inclusive of all arms from all periods. This commenter also suggested that historical controls not be counted in the Number of Arms data item of the Study Design data element, which is specified in proposed § 11.28(a)(1)(v) and defined in proposed § 11.10(b)(5)(ii). We interpreted this comment to refer to ''mutually exclusive reporting arms,'' agree with the commenter, and note that the definition in § 11.10(b)(5)(ii) specifies that ''[f]or a trial with multiple periods or phases that have different numbers of arms, it means the maximum number of arms during all periods or phases.'' We also reiterate, as stated in the preamble of the NPRM, that ''historical controls are not considered to be an 'arm' of a clinical trial and thus are not counted in the number of arms'' (79 FR 69613). After considering this comment, we maintain the proposed definition in the final rule, except the definition clarifies that for a trial with multiple periods or phases

that have different numbers of arms, the ''number of arms'' means the maximum number of arms during ''all periods or phases''.

Arm Information. In § 11.10(b)(5)(iii) of the NPRM, this data item was defined as ''[a] description of each arm of the clinical trial that indicates its role in the clinical trial, provides an informative title, and, if necessary, additional descriptive information to differentiate each arm from other arms in the clinical trial.'' As stated in the NPRM, responsible parties would be required to select from the following list of options for describing the role of each arm in the clinical trial: ''Experimental,'' ''active comparator,'' ''placebo comparator,'' ''sham comparator,'' ''no intervention,'' or ''other.'' The informative title would consist of a label or short name to identify the arm in the clinical trial record (*e.g.,* the name of the experimental intervention used in the arm or placebo). Additional descriptive information would be required if the informative title does not sufficiently differentiate among arms in the clinical trial (*e.g.,* in a clinical trial that compares two different dosages of the same investigational drug, the descriptive information would have to indicate which is the higher dose arm versus the lower dose arm). Even if the informative title and/or additional descriptive information vary sufficiently among the arms of the clinical trial, responsible parties may voluntarily include additional details about the interventions or the arms in this field (79 FR 69613). We received a few comments about Arm Information. One commenter requested that the final rule clarify that a historical-control arm be considered ''other'' from the list of options available for Arm Information. Another commenter asked for a way to distinguish between study designs that incorporate ''concurrent'' and ''nonconcurrent'' controls, which are described in the preamble discussion of the term ''controlled'' in the NPRM. As noted in the preamble of the NPRM, we do not consider historical controls or other types of non-concurrent controls to be arms for the purposes of the Number of Arms data item defined in proposed § 11.10(b)(5)(ii) (79 FR 69613). Because Arm Information is used to describe each arm identified by Number of Arms, the need to identify an arm as ''historical'' or ''nonconcurrent'' should not arise when submitting Arm Information in *ClinicalTrials.gov*. However, if a responsible party wishes to identify and/or describe a historical or non-concurrent control used in the study, we note that such information could be submitted using an optional data item such as Detailed Description. After consideration of these comments, we generally are maintaining the proposed definition in the final rule. However, we are revising it slightly to specify that if more than one arm is specified for the clinical trial, the responsible party must designate the listed intervention(s) to the arm in which they are administered. Therefore, ''arm information'' is defined as ''[a] description of each arm of the clinical trial that indicates its role in the clinical trial, provides an informative title, and, if necessary, additional descriptive information (including which interventions are administered in each arm) to differentiate each arm from other arms in the clinical trial.'' This designation approach (currently implemented using the ''[Arm or Group]/Intervention Cross-Reference'' data element) will allow for continuing to display on *ClinicalTrials.gov* arm and intervention information as a table, helping users understand the relationship between arm information and intervention information.

Allocation. In § 11.10(b)(5)(iv) of the NPRM, this data item was defined as ''[t]he method by which human subjects are assigned to arms in a clinical trial.'' As stated in the NPRM, responsible parties would be required to select from the following limited set of options: ''randomized'' (participants are assigned to intervention groups by chance), or ''nonrandomized'' (participants are expressly assigned to intervention groups through a non-random method, such as physician choice), or ''not applicable'' (for a single-arm study). No ''other'' option was proposed (79 FR 69613). We invited public comment, but did not receive any, therefore, we maintain the proposed definition and approach in the final rule.

Masking. In § 11.10(b)(5)(v) of the NPRM, this data item was defined as ''[t]he party or parties, if any, involved in the clinical trial who are prevented from having knowledge of the interventions assigned to individual human subjects.'' As stated in the NPRM, responsible parties would be required to select from the following limited set of choices for describing which party(ies) is/are masked: ''human subject,'' ''care provider,'' ''investigator,'' and/or an ''outcomes assessor'' (*i.e.,* the individual who evaluates the outcome(s) of interest). No ''other'' option was proposed, but responsible parties would have the ability to provide additional, optional free-text information about other parties who may be blinded in the clinical trial (79 FR 69614). We received no comments, however, for clarity, we are adding to the limited menu of choices ''no masking'' for the responsible party to indicate that the study design does not include masking (*e.g.,* open-label). We otherwise maintain the proposed definition in the final rule.

Single Arm Controlled. In § 11.10(b)(5)(vi) of the NPRM, this data item was defined as ''for a single arm clinical trial only, whether or not the clinical trial is controlled, as specified by the protocol or statistical analysis plan.'' We have deleted this data item in the final rule because the information is no longer necessary to determine whether a clinical trial is ''controlled'' under the definition in § 11.10(a) and therefore an ''applicable drug clinical trial'' or ''applicable device clinical trial'' under the regulations, as discussed in the preamble for § 11.22.

(F) *Study Phase.* In § 11.10(b)(6) of the NPRM, this data element was defined as ''for a clinical trial of a drug, the numerical phase of such clinical trial, consistent with terminology in 21 CFR 312.21, or any successor regulation, such as phase 2 or phase 3, and in 21 CFR 312.85, or any successor regulation, for phase 4 studies.'' Section 402(j)(2)(A)(ii)(I)(ee) of the PHS Act expressly requires, for an applicable drug clinical trial, the ''study phase'' to be submitted as a clinical trial registration information data element, but it does not define the term. As stated in the NPRM, responsible parties would be required to select one response from a limited list of options that includes phases 1, 2, 3, and 4, consistent with the terminology in 21 CFR 312.21 and 21 CFR 312.85. In addition, responsible parties would be able to select from other options that are commonly used in practice: Phase 1/phase 2 (for trials that are a combination of phases 1 and 2; as discussed previously, phase 1/phase 2 studies are not considered phase 1 studies and may be applicable drug clinical trials) and phase 2/phase 3 (for trials that are a combination of phases 2 and 3). No ''other'' option was proposed. Although we are aware that the term ''phase 0'' is used in practice (*e.g.,* to refer to clinical trials that are exploratory in nature and are not designed to evaluate therapeutic or diagnostic intent), any trial that would be referred to as ''phase 0'' meets the definition of a phase 1 trial under FDA regulations (21 CFR 312.21). Therefore, we did not propose to include ''phase 0'' as an option for the Study Phase data element, and responsible parties registering a clinical trial that might be referred to as ''phase 0'' would select ''phase 1'' for the Study Phase (79 FR 69614). We received no comments on

this description and therefore maintain the proposed description in the final rule except that we clarify that ''drug'' means ''drug product.'' We note that study phases are not intended for use in describing clinical trials of devices; therefore, consistent with section 402(j)(2)(A)(ii)(I)(ee) of the PHS Act, responsible parties for applicable device clinical trials would not be required to submit this data element.

(G) *Study Type.* In § 11.10(b)(7) of the NPRM, we defined this data element as ''the type of study for which clinical trial information is being submitted.'' Section 402(j)(2)(A)(ii)(I)(ff) of the PHS Act expressly requires ''study type'' to be submitted as clinical trial information at the time of registration, but it does not define the term. Consistent with practice prior to FDAAA, we stated in the NPRM that responsible parties would be required to select one of the following limited set of options: ''Interventional,'' ''observational,'' or ''expanded access program.'' No ''other'' option was proposed. We expressed our belief that all applicable clinical trials and all other clinical studies that might be registered voluntarily on *ClinicalTrials.gov* could be accurately characterized as either ''interventional'' or ''observational,'' depending on whether human subjects studied are assigned to interventions based on a research protocol (interventional) or whether patients receive interventions as part of routine medical care, and a researcher studies the effect of the intervention (observational). We indicated that we would consider observational studies to include a wide range of non-interventional studies, including retrospective reviews of patient records or relevant literature (79 FR 69614). (See the elaboration of the terms ''applicable device clinical trial'' and ''applicable drug clinical trial'' in Section IV.A.5 of this preamble). We received one comment requesting that we provide clarification by either providing examples or modifying the definition so that it does not use the term being defined. We believe ''type of study'' in the proposed definition is sufficiently clear, particularly with the three options described for the Study Type data element. In addition, the elaboration of the terms ''applicable device clinical trial'' and ''applicable drug clinical trial'' in Section IV.A.5 of this preamble provide further details about interventional and observational studies. We also plan to provide additional guidance, including examples, as needed.

After considering the comments, we maintain the NPRM definition in the final rule, except we clarify that Study Type means ''the nature of the investigation or investigational use for which clinical trial information is being submitted, *e.g.,* interventional, observational.'' We note that a study that is designated ''interventional,'' as that term is defined in this part, may or may not be an applicable clinical trial, depending on whether it meets the other criteria for an applicable clinical trial that are specified in this part. A study that is designated ''observational'' would be an applicable clinical trial only if it is a pediatric postmarket surveillance of a device product as defined in this part. (See the definition of ''pediatric postmarket surveillance of a device product'' in § 11.10, the discussion of § 11.28(b), and the discussion of observational studies in Section IV.A.5 of this preamble). Conversely, any applicable clinical trial other than a pediatric postmarket surveillance of a device product must have a Study Type of ''interventional.'' An applicable clinical trial that is a pediatric postmarket surveillance of a device product could have a Study Type of ''interventional'' or ''observational.'' The term ''expanded access'' is provided as an option for Study Type because responsible parties who are both manufacturers of an investigational drug product (including a biological product) that is available for expanded access use and sponsors of an applicable clinical trial of the investigational product are required to create an expanded access record for the investigational drug product (including a biological product) if such a record does not already exist at the time the applicable clinical trial is registered. As discussed in section IV.A.5 of this preamble, expanded access use is not considered to be an applicable clinical trial. Therefore, the Study Type for all expanded access use is ''expanded access'' (see the discussion of § 11.28(c)).

(H) *Pediatric Postmarket Surveillance of a Device Product.* In § 11.10(b)(8) of the NPRM, we defined the Whether the Study is a Pediatric Postmarket Surveillance of a Device data element to mean ''for a study that includes a device as an intervention and is a pediatric postmarket surveillance of a device, an affirmation that the study is a pediatric postmarket surveillance of a device.'' Although this data element is not explicitly listed in section 402(j) of the PHS Act as part of clinical trial information, we proposed it to identify a subset of applicable device clinical trials. As we noted in the NPRM, the term ''applicable device clinical trial'' is defined, in part, as ''a pediatric postmarket surveillance as required under section 522 of the Federal Food, Drug, and Cosmetic Act'' (see section 402(j)(1)(A)(ii)(II) of the PHS Act). A responsible party would be required to provide this data element only if the study is a pediatric postmarket surveillance of a device product; a responsible party would not be required to submit this data element if the device study is not a pediatric postmarket surveillance of a device product (79 FR 69615). We received no comments addressing this data element. In the final rule, we modify the name of the data element to ''Pediatric Postmarket Surveillance of a Device Product'' to clarify that ''device'' means ''device product'' and modify the definition to clarify that the term refers only to ''a clinical trial or study that includes a U.S. FDA-regulated device product as an intervention'' and is a pediatric postmarket surveillance of a device product ''ordered under section 522 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 369l).'' In the final rule, we also removed from the definition the requirement for an affirmation that the study is a pediatric postmarket surveillance of a device. By indicating that a study is a pediatric postmarket surveillance of a device product, users of the data bank and the Agency will be able to confirm that the study is an applicable device clinical trial. In addition, by combining this information with other submitted clinical trial registration information (*e.g.,* the Study Type data element), the Agency could confirm whether the pediatric postmarket surveillance of a device product is a clinical trial and indicate which other data elements must be submitted at the time of registration. If a pediatric postmarket surveillance of a device product is a clinical trial, the clinical trial registration information data elements set forth in § 11.28(a) will be required to be submitted. If a pediatric postmarket surveillance of a device product is not a clinical trial (*i.e.,* it is a form of observational study, including a retrospective review of patient records or relevant literature), then the clinical trial registration information data elements specified in § 11.28(b) will be required to be submitted.

(I) *Primary Disease or Condition Being Studied in the Trial, or the Focus of the Study.* In § 11.10(b)(9) of the NPRM, we defined this data element as ''the name(s) of the disease(s) or condition(s) studied in the clinical trial, or the focus of the clinical trial, using, if available, appropriate descriptors from the NLM's

MeSH controlled vocabulary thesaurus *http://www.nlm.nih.gov/mesh/,* or terms from another vocabulary, such as the SNOMED CT, that has been mapped to MeSH within the UMLS Metathesaurus, *https://uts.nlm.nih.gov.''* As we noted in the NPRM, section 402(j)(2)(A)(ii)(I)(gg) of the PHS Act expressly requires ''the primary disease or condition being studied, or the focus of the study'' to be submitted as part of clinical trial registration information, but it does not define the term. Section 402(j)(2)(B)(i)(I) of the PHS Act further requires the data bank to be searchable by one or more of eight listed criteria, including ''the disease or condition being studied in the clinical trial, using Medical Subject Headers (MeSH) descriptors.'' To support searching using MeSH descriptors, the primary disease or condition being studied in the clinical trial, or the focus of the study, must be described using either MeSH terminology (*http://www.nlm.nih.gov/mesh/*) or another terminology that has been mapped to MeSH, when available (if the other terminology is mapped to MeSH, the data bank can be searched using MeSH terms and retrieve the correct record(s)) (79 FR 69615). We received no comments on this proposed data element, but we slightly modify the proposed description in the final rule for clarity as follows: ''the name(s) of the disease(s) or condition(s) studied in the clinical trial, or the focus of the clinical trial. Use, if available, appropriate descriptors from NLM's Medical Subject Headings (MeSH) controlled vocabulary thesaurus, or terms from another vocabulary, such as the Systematized Nomenclature of Medicine—Clinical Terms (SNOMED CT), that has been mapped to MeSH within the Unified Medical Language System (UMLS) Metathesaurus.'' We note that this definition is consistent with ''health condition(s) or problem(s) studied'' of the WHO Trial Registration Data Set (version 1.2.1) (WHO data item #12) and ICMJE registration policies [Ref. 2, 73].

(J) *Intervention Name(s).* Under § 11.10(b)(10) of the NPRM, Intervention Name was specified as ''a brief descriptive name used to refer to the intervention(s) studied in each arm of the clinical trial. A non-proprietary name of the intervention must be used, if available. If a non-proprietary name is not available, a brief descriptive name or identifier must be used.'' Section 402(j)(2)(A)(ii)(I)(hh) of the PHS Act expressly requires ''intervention name'' to be submitted as part of clinical trial information at the time of registration, but it does not define the term. As we explained in the NPRM, we believe the purpose of this data element is to enable interested parties to readily identify the intervention(s) being studied in each arm of a clinical trial and compare clinical trials by intervention. While some clinical trials compare a single intervention against a placebo, many compare multiple interventions (*e.g.,* a newly developed drug product versus standard treatment, or different dosages of the same drug product). We believe it is important for the names of all interventions studied in a clinical trial to be submitted to the data bank (79 FR 69616). We received no comments on this proposed data element and therefore are maintaining it in the final rule, although we slightly modify its name to ''Intervention Name(s)'' and specify in the definition that ''it'' refers to ''the intervention'' for clarity. Based on our experience in operating *ClinicalTrials.gov*, we recognize that there are inherent difficulties in determining the level of detail that should be required for naming interventions, especially those without non-proprietary (*i.e.,* generic) names [Ref. 23]. We believe that non-proprietary names must be provided for interventions (*e.g.,* drug products (including biological products) and device products) when available. For interventions for which a non-proprietary name is not available, our prior experience suggests that a brief descriptive name can suffice. In either case, additional descriptive information is often needed to distinguish the intervention(s) under study from other, similar interventions used in practice or studied in the same or other clinical trials. Examples of a brief descriptive name or identifier include a chemical name, company code, or serial number. We note that this description of Intervention Name(s) is consistent with the ''intervention(s)'' of the WHO Trial Registration Data Set (version 1.2.1) (WHO data item #13) and ICMJE registration policies [[Ref. 2, 73].

(K) *Other Intervention Name(s).* In § 11.10(b)(11) of the NPRM, this term was defined as ''other current and former name(s) or alias(es), if any, different from the Intervention Name(s), that the sponsor has used publicly to identify the intervention, including, but not limited to, past or present names such as brand name(s), serial numbers, or chemical descriptions.'' As noted in the NPRM, ''other intervention name(s)'' is a term that is not used in section 402(j) of the PHS Act, but it is proposed as a data element that responsible parties must submit if the sponsor has used more than one name publicly to identify the intervention under study in a clinical trial. Based on our experience operating *ClinicalTrials.gov,* we are aware that interventions often have multiple names, including, for example, a sponsor code name, brand name(s), or a name or identifier from a standard vocabulary, such as RxNorm for drugs (*http://www.nlm.nih.gov/research/umls/rxnorm/index.html*). Accordingly, providing only a single name for each intervention (as is required under the Intervention Name(s) data element) does not necessarily provide enough information to allow users to find and compare all clinical trials in *ClinicalTrials.gov* that involve a specific intervention, as a different clinical trial with the same intervention may have been registered by another responsible party under a different intervention name. Therefore, we noted that we believe that adding a requirement to submit Other Intervention Name(s) improves and does not reduce the clinical trial information available in the data bank. We also noted that this requirement could mean that, in some circumstances (*e.g.,* when the responsible party is a designated principal investigator), the responsible party would need to communicate with the sponsor or the manufacturer of the intervention(s) to determine whether another name has been used publicly. We indicated that we do not believe such additional communication would be frequent or onerous. The proposal would not have required a responsible party to submit names that have not been used publicly because users of *ClinicalTrials.gov* would be unlikely to search for a clinical trial using such names. We asked for comment on this approach (79 FR 69616) and some commenters addressed the Other Intervention Name(s) data element. A few commenters suggested requiring the use of a universally recognized standard, such as the WHO International Nonproprietary Names (INN) or the FDA unique device identifier (UDI). While we agree that the Other Intervention Name(s) data element includes all standardized names, we note that the data element is not limited to only those intervention names that are compliant with a particular naming standard or convention. As stated in the proposed definition, this data element is intended to broadly capture all ''other current and former name(s) or alias(es) . . . that the sponsor has used publicly to identify the intervention.'' Therefore, we clarify that all names, including internationally recognized standard names, must be

submitted for the Other Intervention Name(s) data element.

One commenter indicated that displaying other intervention names would be confusing to the public and suggested that the final rule remove Other Intervention Name(s) as a required data element. Another commenter requested that only the U.S. generic and proprietary names be required for submission. We disagree with both commenters. Because users of *ClinicalTrials.gov* may encounter a number of names for an intervention depending on the source or context (*e.g.,* drug code name), we believe that providing access to all the different public names of an intervention would help users find potentially relevant information. Additionally, requiring responsible parties to provide all public names for an intervention allows the *ClinicalTrials.gov* system to identify and retrieve clinical studies records listing any of the relevant intervention names. After consideration of these comments, we generally maintain this data element as proposed in the final rule. We modify the definition by deleting the phrase ''chemical descriptions'' to avoid any suggestion that chemical descriptions are required to be submitted. Chemical descriptions are, however, an example of another type of name that would be appropriate to include for Other Intervention Name(s).

(L) *Intervention Description.* In § 11.10(b)(12) of the NPRM, we defined this term to mean ''details that can be made public about the intervention, other than the Intervention Name and Other Intervention Name(s), sufficient to distinguish it from other, similar interventions studied in the same or another clinical trial.'' As we described in the NPRM, while this term is not used in section 402(j) of the PHS Act, we proposed it as an additional data element to be submitted as clinical trial information at the time of registration. Based on prior experience, we recognize that the Intervention Name(s) and Other Intervention Name(s) data elements, whether providing information on brand or non-proprietary names, do not always provide enough information to allow potential human subjects or other *ClinicalTrials.gov* users to differentiate among similar interventions used in different arms of a clinical trial, distinguish the intervention used in one clinical trial from a similar intervention used in another clinical trial, or understand the differences between interventions studied in a clinical trial and those used in routine medical practice. For example, a clinical trial might compare two or more dosages of the same drug or two different clinical trials might examine drug-eluting stents that are similar to those used in standard medical practice. To reduce this ambiguity, additional descriptive information about the intervention is needed, such as information about the dosage, dosage form, frequency of administration, route of administration, and/or duration of administration of a drug, or a general description of the device, including how the device functions; the scientific concepts that form the basis for the device; and the significant physical and performance characteristics of the device, such as its key components and the general types of materials used. The submission of such information would enable users (whether subjects, patients, physicians, researchers, or others) to understand key elements of a clinical trial, and compare information among clinical trials. For these reasons, requiring the submission of an intervention description would improve but not reduce the clinical trial information available in the data bank (79 FR 69616). A few commenters suggested that the Agency consider making optional some of the details required to be submitted for the Intervention Description data element; other commenters recommended that the entire data element be considered optional in the final rule. The reasons provided were that such detailed information may contain confidential commercial information and providing such details would be burdensome. The Agency disagrees with these commenters and continues to believe that users of the public site must be able to understand the interventions that are being compared in a trial and how the comparators differ from each other and/or other similar interventions. For example, the Consolidated Standards Of Reporting Trials (CONSORT) guidelines recommend that each intervention, including control interventions, be described thoroughly so that published studies may be understood more clearly [Ref. 93]. The submission of these details at study registration could also give earlier insight to the problem of study sponsors choosing inapprorpriate comparison groups, which can bias study results [Ref. 94]. As specified in the NPRM, the Agency also believes that sufficiently detailed information could be made public without including information that the sponsor may consider sensitive or proprietary (79 FR 69616). While the final rule retains the name of the proposed data element, we have modified the proposed definition by adding an example for clarity as a second sentence. Thus, the final rule defines the term to mean ''details that can be made public about the intervention, other than the Intervention Name(s) and Other Intervention Name(s), sufficient to distinguish it from other, similar interventions studied in the same or another clinical trial. For example, interventions involving drugs may include dosage form, dosage, frequency and duration.'' We clarify that Intervention Description should be sufficiently detailed to differentiate the specified intervention from other similar interventions, but should not include information that the responsible party cannot make public. For example, if the specific dosage of a drug being studied cannot be divulged, a responsible party could instead indicate whether the dosage is higher or lower than that used in an approved or licensed drug or in another arm of the study. If an experimental device uses different material than previous versions of the device, or than other marketed devices, the responsible party could provide a general description of the new material without including its specific formulation.

(M) *Intervention Type.* In § 11.10(b)(13) of the NPRM, Intervention Type was defined as ''for each intervention studied in the clinical trial, the general type of intervention.'' As we pointed out in the NPRM, section 402(j)(2)(A)(ii)(I)(hh) of the PHS Act expressly requires ''intervention type'' to be submitted as part of clinical trial information at the time of registration, but it does not define the term. We further proposed that responsible parties would be required to select one of the following options for each intervention studied: ''drug'' (including placebo), ''device'' (including sham), ''biological/vaccine,'' ''procedure/surgery,'' ''radiation,'' ''behavioral'' (*e.g.,* psychotherapy, lifestyle counseling), ''genetic'' (including gene transfer, stem cell and recombinant DNA), ''dietary supplement'' (*e.g.,* vitamins, minerals), ''combination product'' (combining a drug and device, a biological product and device; a drug and biological product; or a drug, biological product, and device), ''diagnostic test'' (*e.g.,* imaging, in-vitro), and ''other.'' We noted that when the intervention used is a combination product (*e.g.,* drug-eluting stent), the responsible party must select ''combination product'' as the Intervention Type (79 FR 69617). We received one comment requesting clarification by either providing examples or modifying the definition so that it does not use the term being defined. We believe ''type of intervention'' in the proposed definition

is sufficiently clear, particularly with the options described for the Intervention Type data element. We also plan to provide additional guidance as needed.

After considering the comments, we maintain the NPRM definition in the final rule, except that we add ''*e.g.,* drug, biological/vaccine, or device'' as examples for clarification. Note that, as specified in § 11.28(a)(2)(i)(M) of the final rule, selection of an Intervention Type is required for each intervention studied in each arm of the clinical trial. Some clinical trials will therefore include multiple intervention types. As discussed in Section IV.B.2 of this preamble, a clinical trial that studies a drug and a device as separate, independent interventions would list both ''drug'' and ''device'' as Intervention Types and may meet the definitions of both an applicable device clinical trial and an applicable drug clinical trial. If the U.S. FDA-regulated device product studied in such an applicable clinical trial is not approved or cleared by FDA for any use, we would not post clinical trial registration information for that applicable clinical trial prior to the date of approval or clearance of the device product, consistent with § 11.35(b)(2)(i), unless the responsible party indicates, pursuant to § 11.35(b)(2)(ii), that it authorizes such posting. In addition, if the Intervention Type is specified as a ''drug,'' ''biological/vaccine,'' or ''device,'' but both the Studies a U.S. FDA-regulated Device Product and Studies a U.S. FDA-regulated Drug Product data elements are specified as ''no,'' the clinical trial would not be an applicable clinical trial under the definition in § 11.10(a). For this reason, we note that the Intervention Type data element is not used in determining whether a clinical trial is an applicable clinical trial as specified in § 11.22(b).

(N) *Studies a U.S. FDA-regulated Device Product.* In § 11.10(b)(39) of the NPRM, we defined this data element to mean ''a clinical trial that studies a device subject to section 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act.'' As we described in the NPRM, although section 402(j) of the PHS Act does not explicitly require submission of such a clinical trial registration information data element, we proposed to require such a data element using our authority under section 402(j)(2)(A)(iii) of the PHS Act, to assist responsible parties, users of *ClinicalTrials.gov,* and the Agency in determining whether a clinical trial is an applicable device clinical trial, using the approach specified in proposed § 11.22(b)(1). As specified in the elaboration of the definition of an ''applicable device clinical trial'' in Section IV.A.5 of this preamble, one criterion for an applicable device clinical trial is that the clinical trial studies a device product ''subject to section 510(k), 515, or 520(m) of the [FD&C Act].'' It is possible that a clinical trial with an Intervention Type of ''device'' would not be an applicable device clinical trial because the device is not subject to section 510(k), 515, or 520(m) of the FD&C Act. Conversely, it is possible that a clinical trial could be an applicable device clinical trial even if none of the specified Intervention Types is a ''device.'' For example, a clinical trial for which a responsible party indicates the Intervention Type is ''radiation,'' ''genetic,'' or ''procedure'' could in fact be an applicable device clinical trial studying a device product subject to section 510(k), 515, or 520(m) of the FD&C Act (*e.g.,* an x-ray device, a genetic test, or a surgical instrument). If the responsible party has obtained an IDE and submitted an IDE number to *ClinicalTrials.gov,* the clinical trial is considered an applicable device clinical trial as defined in this part. If the responsible party does not submit an IDE number, however, ambiguity would arise because the lack of an IDE number (or an IDE) does not necessarily indicate that a clinical trial is not an applicable device clinical trial. We proposed requiring the Studies an FDA-regulated Device data element in the NPRM to avoid this ambiguity and help ensure that applicable clinical trials can be properly identified. Consistent with the elaboration of the term applicable device clinical trial in Section IV.A.4 of this preamble, we interpreted this definition to mean that the clinical trial studies a device that would require any of the following before it may be legally marketed in the United States: (1) A finding of substantial equivalence under section 510(k) of the FD&C Act, (2) an order under section 515 of the FD&C Act approving a premarket approval application (PMA) for the device, or (3) an HDE under section 520(m) of the FD&C Act. We believe that submission of this information would improve and not reduce the clinical trial information submitted at the time of registration by making it clear to the responsible party, the Agency, and users of *ClinicalTrials.gov* whether a clinical trial without an IDE studies an FDA-regulated device. This information would, in turn, be used in determining whether a clinical trial meets the definition of an applicable device clinical trial, following the approach specified in proposed § 11.22(b)(1). We also noted that, to reduce the data entry burden on responsible parties, *ClinicalTrials.gov* could automatically pre-populate this data field to indicate ''yes'' if a responsible party submits an IDE number as part of the FDA IND or IDE Number data element specified in proposed § 11.10(b)(35) (79 FR 69617).

We received no comments addressing the proposed data element and therefore retain the proposed definition in the final rule, except that the definition clarifies that ''device'' is ''device product'' and includes the applicable U.S.C. statutory citations in the final rule. The name has also been changed from the proposed ''Studies an FDA-regulated Device'' to ''Studies a U.S. FDA-regulated Device Product'' in the final rule for clarity. We also note that we are aware that device products may be used in clinical trials even though they are not the intervention studied in the clinical trial or the experimental variable of interest in the study. For example, clinical trials of procedures involving surgical device products may not be designed to study the effect of those device products. Therefore, when considering whether a clinical trial Studies a U.S. FDA-regulated Device Product a responsible party should consider whether (a) the study is designed to examine the effect or performance of an FDA-regulated device product or differences in the intended use, for example, variations in frequency of use, method of administration, design specifications, and other characteristics (*e.g.,* used in one or more, but not all, arms in a multi-arm study); and/or (b) at least one pre-specified primary or secondary outcome measure reflects a characteristic, effect, or performance of an FDA-regulated device product (*e.g.,* need for replacement or maintenance of the device). As described in the preamble discussion of an applicable device clinical trial in § 11.10(a), a clinical trial of a combination product with a device primary mode of action that otherwise meets the definition of an ''applicable clinical trial'' will be considered an applicable device clinical trial. We note that for such trials, the responsible party must indicate that the trial Studies a U.S. FDA-regulated Device Product.

(O) *Studies a U.S. FDA-regulated Drug Product.* In § 11.10(b)(40) of the NPRM, we defined this data element to mean ''a clinical trial that studies a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to section 351 of the Public Health Services Act.'' As we described in the NPRM, section 402(j) of the PHS Act does not explicitly require submission of such a clinical trial registration

information data element. We proposed to require this data element, however, using our authority under section 402(j)(2)(A)(iii) of the PHS Act to assist responsible parties, users of *ClinicalTrials.gov*, and the Agency in determining whether or not a clinical trial is an applicable drug clinical trial using the approach specified in proposed § 11.22(b)(2). As specified in the elaboration of the definition of an ''applicable drug clinical trial'' in Section IV.A.5 of this preamble, one criterion for an applicable drug clinical trial is that the clinical trial studies a drug ''subject to section 505 of the [FD&C] Act or [a biological product subject] to section 351 of [the PHS] Act.'' We noted that it is possible that a clinical trial with an Intervention Type of ''drug'' or ''biological/vaccine'' would not be an applicable drug clinical trial because the drug product is not subject to section 505 of the FD&C Act (*e.g.,* a non-prescription drug product that is marketed under an over-the-counter drug monograph) and/or the biological product is not subject to section 351 of the PHS Act. Conversely, we indicated that it is possible that a clinical trial could be an applicable drug clinical trial even if the responsible party does not select ''drug'' or ''biological/vaccine'' as the Intervention Type. A clinical trial for which the responsible party indicates the Intervention Type to be ''dietary supplement'' or ''genetic'' or ''procedure'' could in fact be an applicable drug clinical trial studying a drug product subject to section 505 of the FD&C Act or a biological product subject to section 351 of the PHS Act. For example, a product otherwise marketed as a dietary supplement could be studied for the treatment of cancer, or a genetic trial could study a gene therapy. If the responsible party has obtained an IND and submitted an IND number to *ClinicalTrials.gov*, the clinical trial would generally be an applicable drug clinical trial as defined in the NPRM. If the responsible party does not submit an IND number, however, ambiguity would arise because the lack of an IND number (or an IND) does not necessarily indicate that a trial is not an applicable drug clinical trial. To avoid this ambiguity and help ensure that applicable clinical trials can be properly identified, we proposed to require a responsible party to specifically indicate whether a clinical trial studies an FDA-regulated drug by submitting the Studies an FDA-regulated Drug data element. Consistent with the elaboration of the term ''applicable drug clinical trial'' in the NPRM, we interpreted this definition to mean that the clinical trial studies a drug that is the subject of an approved NDA or BLA or that would require an approved NDA or BLA to be legally marketed in the United States. We noted in the NPRM our belief that submission of this information would improve, and not reduce, the clinical trial information submitted at the time of registration by making it clear to the responsible party, the Agency, and users of *ClinicalTrials.gov* whether a clinical trial without an IND studies an FDA-regulated drug product (including a biological product). This information would, in turn, be used in determining whether a clinical trial meets the definition of an ''applicable drug clinical trial,'' following the approach specified in proposed § 11.22(b)(2). To reduce the data entry burden on responsible parties, we noted that *ClinicalTrials.gov* could automatically pre-populate this data field to indicate ''yes'' if a responsible party submits an IND number as part of the FDA IND or IDE Number data element specified in proposed § 11.10(b)(35) (79 FR 69618).

We received no comments addressing the proposed data element and therefore retain the proposed definition in the final rule, except that the definition clarifies that ''drug'' is ''drug product'' and includes the applicable U.S.C. statutory citations in the final rule. However, the name has been changed from ''Studies an FDA-regulated Drug'' in the NPRM to ''Studies a U.S. FDA-regulated Drug Product'' in the final rule for clarity. We also note that we are aware that a clinical trial may include an FDA-regulated drug product even though the drug product is not a variable of interest. For example, a clinical trial of a device product may involve the surgical insertion of the device product under anesthesia, but the anesthesia drug product is not studied in the clinical trial. In determining whether a clinical trial studies a U.S. FDA-regulated drug product, a responsible party should consider whether (a) the clinical trial is designed to examine the effect of the FDA-regulated drug product(s) or of differences in the intended use, including differences in dosing, frequency of use, or route of administration; and/or (b) at least one of the pre-specified primary or secondary outcome measures reflects a characteristic or effect of the FDA-regulated drug product(s). As described in the preamble discussion of applicable drug clinical trial in § 11.10(a), a clinical trial of a combination product with a drug primary mode of action will be considered an applicable drug clinical trial. We note that for such trials, the responsible party must indicate that the trial Studies a U.S. FDA-regulated Drug Product.

(P) *Device Product Not Approved or Cleared by U.S. FDA.* In proposed § 11.10(b)(14), we defined U.S. FDA Approval, Licensure, or Clearance Status to mean ''for each drug or device studied in the clinical trial, whether that drug or device is approved, licensed, or cleared by the U.S. Food and Drug Administration for any use.'' Although section 402(j) of the PHS Act does not explicitly require that such a data element be submitted as part of clinical trial information, we proposed it to help ensure that the data bank operates in compliance with statutory requirements, *e.g.,* knowledge of the approval or clearance status of a device is necessary to determine when clinical trial registration information submitted for an applicable device clinical trial may be posted publicly in the data bank (see section 402(j)(2)(D)(ii) of the PHS Act.) We indicated that this information would also be helpful for users of *ClinicalTrials.gov*, including potential participants, who may wish to know whether or not the product(s) under study have been approved, licensed, or cleared for the use studied in the clinical trial. Requiring submission of the approval, licensure, or clearance status for each drug or device studied in an applicable clinical trial would therefore improve and not reduce the clinical trial information available in the data bank, consistent with section 402(j)(2)(A)(iii) of the PHS Act for proposed modifications to clinical trial registration information. We also stated in the NPRM that we would require responsible parties to select a response from the following limited list of choices: ''for studied use(s)'' (the drug, biological product, or device is approved, licensed, or cleared for the use studied in the clinical trial), ''for other use(s)'' (the drug, biological product, or device is approved, licensed, or cleared for use(s) other than those studied in the clinical trial, *e.g.,* the clinical trial studies a new use of the product), or ''No'' (the product has not been approved, licensed, or cleared for any use). No ''other'' option was proposed, but a responsible party would also be able to provide additional, optional free-text information to further describe the approval, licensure, or clearance status (*e.g.,* to indicate that the product has been approved in another dose or dosage form, or to list the indications for which it has been approved). We invited public comment

on whether the set of proposed options is sufficient (79 FR 69618).

Some commenters addressed the proposed U.S. FDA Approval, Licensure, or Clearance Status data element. One commenter requested clarification on whether more information than the FDA approval, licensure, or clearance status would be required for this data element, while another commenter recommended that the Agency itself submit information for this data element. In reviewing these comments and assessing ways to reduce reporting burden where possible, we reconsidered the proposed approach of requiring the FDA approval, licensure, or clearance status information for each product studied in the clinical trial. A separate data element about the approval, licensure, or clearance status for each drug product, biological product, or device product studied in an applicable clinical trial is, for the most part, not necessary to implement these regulations, because that information is provided via other data elements, when necessary. For example, responsible parties will notify the Agency that they are seeking ''initial'' approval, licensure or clearance of a product or approval, licensure, or clearance of a ''new use'' for a product studied in the trial by submitting a certification for delayed submission of results information in accordance with § 11.44(b) and 11.44(c), respectively. A key exception, however, is the need for *ClinicalTrials.gov* to identify applicable device clinical trials that study a device product that has not been previously approved or cleared in order to delay public posting of the submitted clinical trial registration information, as specified in § 11.35(b)(2)(i). Therefore, the final rule replaces the proposed U.S. FDA Approval, Licensure, or Clearance Status data element with the Device Product Not Approved or Cleared by U.S. FDA data element in § 11.28(a)(2)(i)(P), which is defined in § 11.10(b)(14) of the final rule to mean ''that at least one device product studied in the clinical trial has not been previously approved or cleared by FDA for one or more uses.'' As discussed below, this data element must be updated not later than 15 calendar days after a change in approval or clearance status of one or more of the device products studied in the applicable clinical trial.

A responsible party would only be required to complete this data element for a record in which ''Yes'' is selected as the response to the Studies a U.S. FDA-regulated Device Product data element in § 11.28(a)(2)(i)(N). We would require responsible parties to select a response from the following limited list of choices: ''Yes'' (at least one studied FDA-regulated device product has not been previously approved or cleared by FDA for one or more uses and therefore the applicable device clinical trial may be subject to the delayed posting requirements specified in § 11.35(b)(2)(i)) or ''No'' (all studied FDA-regulated device products have been previously approved or cleared by FDA for at least one use and therefore the applicable device clinical trial is not subject to the delayed posting requirement specified in § 11.35(b)(2)(i)).

We included the word ''product'' in the name of the Device Product Not Approved or Cleared by U.S. FDA data element in § 11.28(a)(2)(i)(P) to clarify that, as explained in Section IV.C.3, the Agency in the final rule is focusing on the device ''product'' rather than the device ''type'' when determining which PMA approvals or 510(k) clearances are considered ''initial'' approvals or clearances versus approvals or clearances of a ''new use.'' For example, with respect to 510(k) clearances, the Agency is interpreting ''initial clearance'' in the final rule to pertain to the clearance of a manufacturer's original 510(k) submission for a particular device product whereas ''clearance of a new use'' of a device pertains to the clearance of the same manufacturer's subsequent 510(k) submission for an additional use for the same device product. The term ''manufacturer'' means a manufacturer who is the sponsor of the applicable clinical trial.

This interpretation subjects clinical trial registration information for more devices to delayed posting under section 402(j)(2)(D)(ii)(I) of the PHS Act as compared with the NPRM approach, because each individual device manufacturer seeking initial clearance of its device product would be subject to delayed posting of its clinical trial registration information, as specified in § 11.35(b)(2)(i) of the final rule, rather than only the first manufacturer to obtain clearance for the device type. Consistent with this interpretation, under the definition of ''Device Product Not Approved or Cleared by U.S. FDA,'' if a manufacturer's original 510(k) submission for its particular device product has not been previously cleared, then that manufacturer's device product would be considered a ''device product not cleared by FDA,'' even if another manufacturer has already obtained 510(k) clearance of its device product within the same product type.

A few commenters suggested that the final rule include an option for providing information about the use for which the product has been approved, and additional commenters requested the addition of the option ''Approved but not for use being studied.'' We agree that choices other than the three proposed in the NPRM (*i.e.,* ''for studied uses(s),'' ''for other uses,'' and ''no'') could provide other useful information about a product's approval status. However, because of changes to the data element in the final rule (to indicate ''whether at least one device product studied in the clinical trial has not been previously approved or cleared by FDA for one or more uses,'' as described below) the options proposed by the commenters for specifying the approval, licensure, or clearance status of each studied drug product or device product will no longer be necessary. Another commenter requested that the final rule require the submission of information about the particular approved, licensed, or cleared uses of each product using a standardized terminology to ensure the usefulness and consistency of this information within and across study records. We note that section 402(j)(3)(A)(ii) of the PHS Act requires *ClinicalTrials.gov* to link to information about approved, licensed, or cleared products available on the FDA Web site (*e.g.,* FDA advisory committee meeting summaries, public health advisories, and action package for approval documents) as well as citations from the published literature and structured product labels in NLM's PubMed (*http://www.ncbi.nlm.nih.gov/pubmed/*) and DailyMed (*https://dailymed.nlm.nih.gov/dailymed/*) databases, respectively.

(Q) *Post Prior to U.S. FDA Approval or Clearance.* This data element was neither specified as clinical trial registration information in section 402(j)(2)(A)(ii) of the PHS Act nor proposed in the NPRM. We define the term in § 11.10(b)(40) of the final rule to mean ''for an applicable device clinical trial of a device product that has not been previously approved or cleared, the responsible party indicates to the Director that it is authorizing the Director, in accordance with § 11.35(b)(2)(ii), to publicly post its clinical trial registration information, which would otherwise be subject to delayed posting, as specified in § 11.35(b)(2)(i), prior to the date of FDA approval or clearance of its device product.'' We also list the data element as a component of clinical trial registration information in § 11.28(a)(2)(i)(Q) in accordance with the statutory authority in section 402(j)(2)(A)(iii) of the PHS Act, which

permits the Secretary to ''modify the requirements for clinical trial [registration] information'' by regulation, provided that ''such a modification improves and does not reduce such clinical trial information.'' The Post Prior to U.S. FDA Approval or Clearance data element is needed to allow a responsible party for an applicable clinical trial of a device product that is unapproved or uncleared to indicate to the Director that it is authorizing the Director to publicly post on *ClinicalTrials.gov* its clinical trial registration information, which would otherwise be subject to delayed posting as specified in § 11.35(b)(2)(i), prior to the date of approval or clearance of the product, pursuant to § 11.35(b)(2)(ii). Otherwise, all such trials are subject to the posting deadline specified in § 11.35(b)(2)(i), which states that the Director will post publicly the clinical trial registration information, except for certain administrative data, not earlier than the date of FDA approval or clearance of the device product (see the preamble discussion of § 11.35 for further details). To reduce data submission burden, a responsible party would have this option if the Studies a U.S. FDA-regulated Device Product and the Device Product Not Approved or Cleared by U.S. FDA data elements indicate that at least one studied device product has not been approved or cleared by FDA.

(R) *Product Manufactured in and Exported from the U.S.* In § 11.10(b)(15) of the NPRM, we proposed the following definition for the Product Manufactured in the U.S. data element: ''For a drug or device studied in a clinical trial, whether or not the drug or device is manufactured in the U.S. or one of its territories.'' Although section 402(j) of the PHS Act does not explicitly require that such a data element be submitted as part of clinical trial information, we proposed to include it, using our authority under section 402(j)(2)(A)(iii) of the PHS Act to allow users to determine whether a registered clinical trial is an applicable clinical trial. As explained in the definitions of ''applicable device clinical trial'' and ''applicable drug clinical trial,'' the NPRM noted that even if a clinical trial is being conducted entirely outside of the United States or one of its territories, it is still an applicable clinical trial when the drug product or device product is manufactured in the United States or one of its territories. We noted that a drug product or device product manufactured in the United States or one of its territories is subject to regulation under the FD&C Act, even if it is exported for study in another country (see, for example, 21 CFR 312.110 and section 802 of the FD&C Act). Therefore, we proposed that information indicating whether each intervention studied in a clinical trial is manufactured in the United States or one of its territories would be essential in some situations for determining whether such trial is subject to FDA jurisdiction and meets the definition of an ''applicable clinical trial.'' We indicated that including this information in the data bank would improve and not reduce clinical trial information by publicly providing data necessary to determine whether such trial is an applicable clinical trial (79 FR 69618). We did not receive any public comments on this proposed data element, but we have modified the definition in the final rule. In assessing ways to reduce reporting burden where possible, we reconsidered the proposed requirement for United States product manufacturing information for each drug product (including a biological product) or device product studied in a clinical trial. To determine whether a clinical trial that is not conducted under an IND or IDE and that does not have any study facilities in the United States or its territories meets the definition of an ''applicable clinical trial,'' the Agency, responsible parties, and the public only need information about whether at least one drug product (including biological product) or device product was manufactured in the United States and exported for research. Therefore, we renamed the data element ''Product Manufactured in and Exported from the U.S.'' in § 11.28(a)(2)(i)(R) to clarify that the intent is to identify a U.S.-manufactured product that is exported for research purposes. Additionally, we clarify that ''drug'' means ''drug product'' and ''device'' means ''device product.'' In § 11.10(b)(15) of the final rule, we define this data element to mean ''that any drug product (including a biological product) or device product studied in the clinical trial is manufactured in the United States or one of its territories and exported for study in a clinical trial in another country.'' To reduce data submission burden, a responsible party would be required to complete this data element only if the entry submitted for the U.S. Food and Drug Administration IND or IDE Number data element indicates that there is no IND or IDE for the clinical trial, and the entry(ies) for the Facility Information data element include no facility locations in the United States or its territories.

(S) *Study Start Date.* In § 11.10(b)(16) of the NPRM, we defined Study Start Date to mean: ''the estimated date on which the clinical trial will be open to enrollment of human subjects. If the clinical trial has enrolled the first human subject, the actual date on which the first human subject was enrolled.'' Section 402(j)(2)(A)(ii)(I)(ii) of the PHS Act expressly requires ''study start date'' to be submitted as clinical trial information at the time of registration, but it does not define the term. Section 402(j)(2)(C)(ii) of the PHS Act and proposed § 11.24(a) generally required that clinical trial registration information be submitted to *ClinicalTrials.gov* not later than 21 calendar days after the first human subject is enrolled in the clinical trial. In practice, however, many responsible parties submit clinical trial registration information to *ClinicalTrials.gov* before the first subject is enrolled. In some cases, at the time the clinical trial is registered, the responsible party may not have information about when the first subject will be enrolled or was enrolled (*e.g.,* in a large multi-site trial) but may only know when the clinical trial was or will be opened for enrollment. To account for these potential scenarios, we proposed that responsible parties be required to provide an estimated study start date (*i.e.,* the estimated date on which the clinical trial will be open to enrollment of human subjects), unless and until the responsible party knows the actual study start date (*i.e.,* the actual date on which the first human subject is enrolled). The responsible party would be required to update the Study Start Date data element to reflect the actual study start date not later than 30 calendar days after the first human subject is enrolled, consistent with proposed § 11.64. We suggested in the NPRM that providing the estimated study start date to the public, even before the first subject is enrolled, has important benefits to potential human subjects because it will allow them to know when a clinical trial will likely be open to enrollment. We clarified that the Study Start Date must include the day, month, and year (79 FR 69619).

We received comments on this definition. Several commenters requested that we change the term ''Study Start Date'' to ''Date of First Enrolled Participant'' to avoid confusion with other contexts, such as those related to human subjects protection and IRB oversight, in which the study start date is considered to be when the study is first approved by the IRB and is recruiting. Another comment stated

that the WHO Trial Registration Data Set, defines study start date as the date of first enrollment. One commenter requested that we change the definition of ''Study Start Date'' to ''date of first enrollment'' for consistency with these other policies. Another comment asserted that ICMJE, WHO, FDA, and EMA consider the study start date to be the ''First-Patient-First-Visit,'' which is the first participant's anticipated or actual enrollment date, rather than when the trial is first opened to enrollment. Another commenter acknowledged that our definition requires the Study Start Date to be updated with the ''First-Patient-First-Visit'' (*i.e.,* actual enrollment date) but stated that the other, estimated date on which the clinical trial will be open to enrollment is inconsistent with these other study start date definitions. The commenter requested that we change the definition to ''First-Patient-First-Visit.'' After considering these comments, we maintain the proposed definition for Study Start Date in § 11.10(b)(16) of the final rule, with slight modifications for consistency of phrasing with similar data elements concerning when the responsible party would update the data element with the actual enrollment date. As such, we define Study Start Date as ''the estimated date on which the clinical trial will be open for recruitment of human subjects, or the actual date on which the first human subject was enrolled.'' If the estimated date is used, the responsible party must update the Study Start Date data element to the actual date on which the first human subject was enrolled. We also decline to define Study Start Date as only the ''First-Patient-First-Visit'' or actual enrollment date. The definition already incorporates the actual enrollment date, which the responsible party will use when the first subject has been enrolled. By including the date when recruitment opens and the date of first enrollment, we believe the definition maintains consistency with prior practice at *ClinicalTrials.gov* and addresses commenters' request to document the date of first human subject enrollment as in the WHO Trial Registration Data Set. As stated in the NPRM, we believe that providing the estimated study start date to the public, even before the first subject is enrolled, has important benefits to potential human subjects because it will provide them with the date on which a clinical trial will likely be open to enrollment. To minimize the burden associated with this requirement and to reflect that it is an estimated date, the date may be provided as ''month, year'' when estimated and updated to ''day, month, year'' when actual. We also note that, as discussed above, the final rule modifies the proposed definition of ''enroll or enrolled,'' a component of the definition of Study Start Date (see Section IV.A.5 of this preamble). We note that if a clinical trial is registered with an estimated study start date but the clinical trial is then halted before enrolling the first subject (*e.g.,* because of difficulties in recruitment or loss of funding), the responsible party would not be expected to update the study start date. Instead, the responsible party would be expected to update the Overall Recruitment Status data element defined in § 11.10(b)(25) and specified in § 11.28(a)(2)(ii)(E) to indicate that the clinical trial has been ''withdrawn,'' as such term is used for the purpose of this regulation, and update the Why Study Stopped data element defined in § 11.10(b)(26) and specified in § 11.28(a)(2)(ii)(F).

We note that, as stated in § 11.22(a)(3), an applicable clinical trial, other than a pediatric postmarket surveillance of a device product that is not a clinical trial, is considered to be initiated on the date on which the first human subject is enrolled. Therefore, we consider the actual Study Start Date to be the date of initiation for an applicable clinical trial other than a pediatric postmarket surveillance of a device product that is not a clinical trial.

(T) *Primary Completion Date.* In § 11.28(a)(1)(xiv) of the NPRM, we proposed that when registering a clinical trial, a responsible party must submit the Completion Date for the clinical trial, which was defined in proposed § 11.10(b)(17) of the NPRM as ''the estimated completion date. Once the clinical trial has reached the completion date, the responsible party must update the Completion Date data element to reflect the actual completion date.'' Section 402(j)(2)(A)(ii)(I)(jj) of the PHS Act requires the responsible party to submit information on the ''expected completion date'' of an applicable clinical trial when registering a clinical trial. We noted in the NPRM that the public availability of information about the expected primary completion date (*i.e.,* the expected completion date) is important for an ongoing clinical trial because it provides an indication of the relative progress of the clinical trial and the expected date on which results information may be submitted to the data bank because section 402(j)(3)(c)(i) of the PHS Act requires that, in general, clinical trial results information be submitted not later than 1 year after the earlier of the estimated completion date of the applicable clinical trial or the actual completion date of the applicable clinical trial. We note that certain exceptions apply to this general deadline for the submission of clinical trial results information (see discussion of § 11.44). In addition, we interpreted the phrase ''estimated completion date,'' as such term is used in section 402(j)(3)(c)(i)(I) of the PHS Act, to have the same meaning as ''expected completion date,'' as such term is used in section 402(j)(2)(A)(ii)(I)(jj) of the PHS Act, because both indicate the date on which the responsible party anticipates that the clinical trial will be completed in relation to the primary outcome measures. In addition, we expressed our belief that it is important for users to have information about the actual completion date of a clinical trial, so they know when clinical trial results information would ordinarily be due under section 402(j)(3)(c)(i) of the PHS Act and proposed § 11.44(a), absent certain specified circumstances in which the submission of clinical trial results information may be delayed. Because clinical trial results information generally is required under section 402(j)(3)(c)(i) of the PHS Act and under proposed § 11.44 to be submitted not later than 1 year after the estimated or actual completion date, whichever is earlier, we expressed our belief that it is important for the Completion Date data element to be updated promptly after the completion date is reached. We proposed to require the responsible party to take the following steps with regard to the Completion Date data element: (1) Provide a reasonable estimated completion date at the time of registration; (2) update the estimated completion date at least once every 12 months during the course of the clinical trial, in accordance with proposed § 11.64(a)(2), if the estimate changes; and (3) update the Completion Date information to indicate the actual completion date not later than 30 calendar days after the clinical trial reaches its completion date, in accordance with proposed § 11.64(b)(1)(viii) (79 FR 69619).

Commenters expressed concern about possible confusion and misinterpretation among responsible parties and the public resulting from the proposed data element name and uniformly suggested replacing ''completion date'' with ''primary completion date'' or ''primary outcome measure completion date,'' with several noting that *ClinicalTrials.gov* has used the term ''primary completion date'' since the enactment of FDAAA. We

agree with these comments and note that the Primary Completion Date data element was created in response to section 402(j) of the PHS Act to avoid confusion with the Study Completion Date data element, which existed prior to the law and is currently an optional data element. Furthermore, the final rule in § 11.28(a)(2)(i)(U) adds the Study Completion Date data element as a component of clinical trial registration information. In response to these comments and taking into consideration statutory requirements, we rename the Completion Date data element ''Primary Completion Date'' in § 11.28(a)(2)(i)(T) of the final rule and use the term ''Primary Completion Date'' throughout the final rule for clarity. Primary Completion Date is defined in § 11.10(b)(17) of the final rule to mean ''the estimated or actual primary completion date. If an estimated primary completion date is used, the responsible party must update the Primary Completion Date data element once the clinical trial has reached the primary completion date to reflect the actual primary completion date.'' We also note that the term ''completion date'' in § 11.10(a) of the final rule states, in part, that ''[f]or purposes of this part, completion date is referred to as 'primary completion date.'''

(U) *Study Completion Date.* This data element was neither specified as clinical trial registration information in section 402(j)(2)(A)(ii) of the PHS Act nor proposed in the NPRM. We define the term ''study completion date'' in § 11.10(a) of the final rule to mean ''for a clinical trial, the date the final subject was examined or received an intervention for purposes of final collection of data for the primary and secondary outcome measures and adverse events (*e.g.,* last subject's last visit), whether the clinical trial concluded according to the pre-specified protocol or was terminated.'' The final rule also lists Study Completion Date as a required registration data element under § 11.28(a)(2)(i)(U) and specifies the data element definition in § 11.10(b)(41) as ''the estimated or actual study completion date. Once the clinical trial has reached the study completion date, the responsible party must update the Study Completion Date data element to reflect the actual study completion date in accordance with § 11.64(a)(1)(ii)(J).'' We have included the study completion date as a component of clinical trial registration information in accordance with the statutory authority in section 402(j)(2)(A)(iii) of the PHS Act, which permits the Secretary to ''modify the requirements for clinical trial [registration] information'' by regulation, provided that ''such a modification improves and does not reduce such clinical trial information.'' We believe that Study Completion Date is helpful to indicate to the Agency, responsible parties, and the public when all primary and secondary outcome measures and collection of all adverse event information, as specified in the protocol, will be completed and when final data collection for all primary and secondary outcomes and all adverse events has occurred. Some commenters requested that a mechanism be included in the PRS to make clear to responsible parties when they have fulfilled all obligations to update the study record as specified in proposed § 11.64(a)(3) and that no further updates are required. Several other commenters suggested that ''completion date,'' defined in proposed § 11.10(a), be redefined to mean ''final visit/final patient'' or ''final visit/final patient for all outcome measures.'' Following an internal review of the proposed rule, we also note that while proposed § 11.44(d) described the procedure for submitting partial results information, it did not specify how to determine when the responsible party's obligation under subpart C is fulfilled. While the Study Completion Date does not specify when these obligations are fulfilled per se, it does provide the minimum amount of information needed to make such a determination based on when all of the data for a trial is to be collected. Note that § 11.64(a)(1)(ii)(J) of the final rule requires the responsible party to update the Study Completion Date within 30 calendar days after the clinical trial reaches its actual study completion date.

(V) *Enrollment.* We defined this data element in § 11.10(b)(18) of the NPRM as ''the estimated total number of human subjects to be enrolled or target number of human subjects in the clinical trial.'' Section 402(j)(2)(A)(ii)(I)(kk) of the PHS Act expressly requires submission of ''the target number of subjects'' to be enrolled in an applicable clinical trial, but this phrase is not defined. We expressed our belief that this data element is intended to describe the intended or estimated size of the clinical trial, in terms of the estimated total number of human subjects (including healthy volunteers) or target number of human subjects to be enrolled in the clinical trial. We therefore proposed in § 11.28(a)(1)(xx) of the NPRM to require the submission of enrollment information at the time of registration (79 FR 69620). We received a few comments addressing the Enrollment data element. One commenter suggested that the final rule require submission of information about target enrollment goals by gender, age, and race/ethnicity during registration but did not provide any specific justification or evidence that such information is necessary for registration. We note that the clinical trials results information submission requirements under Demographic and baseline characteristics in proposed § 11.48(a)(2)(iii) included the reporting of ''age, gender, and any other measure(s) that were assessed at baseline . . .'' and the final rule further requires the submission of baseline measure information by race and ethnicity, if collected during the clinical trial. *ClinicalTrials.gov* also provides pre-formatted categories that enable responsible parties to submit common demographic characteristics, including age, sex/gender, race, ethnicity, and region of enrollment (if assessed at baseline), to facilitate comparison across study records. Another commenter suggested requiring the listing of the targeted and actual numbers of subjects enrolled in each trial. Two specific required registration data elements proposed in the NPRM, and combined in the final rule, address this comment. The Enrollment data element specified in proposed § 11.28(a)(1)(xx) is defined in proposed § 11.10(b)(18) as ''the estimated total number of human subjects to be enrolled or target number of human subjects in the clinical trial,'' and the Actual Enrollment data element specified in proposed § 11.28(a)(2)(vii) is defined as ''for a clinical trial for which recruitment of human subjects has terminated or completed, the actual number of human subjects enrolled in the clinical trial'' in proposed § 11.10(b)(27). After consideration of these comments, we maintain the proposed name of the Enrollment data element in the final rule, but we combine it with the proposed Actual Enrollment data element for convenience and consistency with the format on *ClinicalTrials.gov* prior to this rule. We clarify that with the approach in the final rule, the estimated number of human subjects to be enrolled will be retained, to allow for later display of both the estimated and actual total number of human subjects enrolled in the clinical trial. We have therefore changed the definition of Enrollment to ''the estimated total number of human subjects to be enrolled (target number) or the actual total number of human subjects that are enrolled in the clinical

trial. Once the trial has reached the primary completion date, the responsible party must update the Enrollment data element to reflect the actual number of human subjects enrolled in the clinical trial.'' We expect that the estimated or target enrollment for a clinical trial may change before or during the clinical trial (*e.g.,* as recruitment continues). Consistent with section 402(j)(4)(C) of the PHS Act and § 11.64(a)(1), a responsible party would be required to update the Enrollment data element not less than once every 12 months, if the anticipated or target enrollment for the clinical trial changes. This update would be in addition to the requirement in § 11.64(a), described in Section IV.D.3, that a responsible party submit the actual enrollment when the clinical trial has reached its primary completion date, *i.e.,* when the Primary Completion Date of the trial is changed to ''actual.'' This requirement is intended to provide users of *ClinicalTrials.gov* with additional information on the total number of participants enrolled in the clinical trial, which may differ from the target enrollment. (See § 11.64(a) and the discussion of Primary Completion Date'' for a discussion of this requirement.) We also note that ''enrolled,'' as defined in § 11.10(a) of the final rule, means ''a human subject's, or their legally authorized representative's, agreement to participate in a clinical trial following completion of the informed consent process, as required in 21 CFR part 50 and/or 45 CFR part 46, as applicable. For the purposes of this part, potential subjects who are screened for the purpose of determining eligibility for a trial, but do not participate in the trial, are not considered enrolled, unless otherwise specified by the protocol.'' In addition, we note that in response to comments on the update requirements in § 11.64, the Enrollment data element must be updated at the time the Primary Completion Date data element is updated to ''actual'' instead of at the time after enrollment closes.

(W) *Primary Outcome Measures and (X) Secondary Outcome Measures* are data elements expressly required by section 402(j)(2)(A)(ii)(I)(ll) of the PHS Act to be submitted as part of clinical trial information at the time of registration. Definitions of the terms ''outcome measure'', ''primary outcome measure'', and ''secondary outcome measure'' are provided and elaborated on in the preamble and subpart A of the final rule. However, section 402(j) of the PHS Act does not specify what specific information about primary and secondary outcome measures must be submitted to *ClinicalTrials.gov* at the time of registration. Under proposed § 11.28(a)(1)(xxi) and (xxii) of the NPRM, responsible parties would be required to submit the information specified in proposed § 11.10(b)(19) and (20) for each primary or secondary outcome measure in their clinical trials, namely the following: (1) The name of the specific outcome measure (*e.g.,* systolic blood pressure), (2) a description of the metric used to characterize the specific outcome measure (*e.g.,* mean value of systolic blood pressure), and (3) the time point(s) at which the measurement is assessed for the specific metric used (*e.g.,* 24 weeks after initiation of treatment). We noted in the NPRM that these requirements are consistent with the WHO Trial Registration Data Set (version 1.2.1), which specifies that each outcome include the name of the outcome, the metric or method of measurement used, and the time point(s) of primary interest. Furthermore, based on our experience in operating *ClinicalTrials.gov*, we expressed our belief that these three elements are key attributes of an outcome measure. Not only may certain outcome measures be assessed in different ways (*e.g.,* systolic blood pressure can be measured as a mean value at a specific time point or as a change from baseline), but also a single clinical trial may assess a single attribute at multiple points in time (*e.g.,* systolic blood pressure may be measured 3 months, 6 months, and 12 months after beginning treatment). Each of these would be considered a different outcome measure. We noted that ensuring that the primary and secondary outcome measures include descriptions of the measures and the time points of assessment is therefore necessary for differentiating between similar measures and for subsequently ensuring that results information is provided for all of them and in a manner that is consistent with the way in which they were pre-specified in the registry. This approach would also ensure that any changes in the outcome measure are recorded as updates to the registration information, consistent with the purpose of the data bank ''to track subsequent progress of clinical trials,'' section 402(j)(2)(A)(i) of the PHS Act (79 FR 69620).

One commenter cited findings of that commenter's research [Ref. 14] and recommended that the final rule require responsible parties to submit information on whether each outcome measure is defined in terms of a noninferiority, superiority, or equivalence hypothesis and associated information about the noninferiority or equivalence margin with relevant calculations and justification of margin selection as free-text descriptions in a new sub-element associated with each reported outcome measure. While we agree with the commenter on the potential value of this information, we note that the information should be available with the reporting of outcomes with results information under § 11.48. We do not believe that the benefits of reporting this information at registration outweighs the burden on responsible parties for reporting these details at that time. We will continue, however, to evaluate ways to accommodate this and other information related to the SAP as optional structured data elements in *ClinicalTrials.gov*. Responsible parties are able to submit this information voluntarily during registration as part of the Detailed Description data element. We also note that, during results reporting for any statistical analysis that is considered scientifically appropriate, the following information is required to be submitted: ''for a non-inferiority or equivalence test, a description of the analysis that includes, at minimum, the power calculation and non-inferiority or equivalence margin'' (see § 11.48(a)(3)(v)). After considering this comment, we maintain the proposed definition in the final rule.

(ii) Recruitment Information

(A) *Eligibility Criteria.* In § 11.10(b)(21) of the NPRM, Eligibility Criteria was described as ''a limited list of criteria for selection of human subjects to participate in the clinical trial, provided in terms of inclusion and exclusion criteria and suitable for assisting potential human subjects in identifying clinical trials of interest.'' Section 402(j)(2)(A)(ii)(II)(aa) of the PHS Act expressly requires ''eligibility criteria'' to be submitted for registration on *ClinicalTrials.gov*, but it does not define the term. In the NPRM we expressed our belief that the purpose of this data element is to enable users of the data bank to determine key characteristics of potential participants in the clinical trial and assist prospective participants in identifying clinical trials that may be of interest. Consistent with the stated objective of section 402(j)(2)(A)(i) of the PHS Act to ''enhance patient enrollment,'' we interpreted the requirement to include an ''Eligibility Criteria'' data element as part of clinical trial registration information to refer to information that can be of practical use to prospective participants who wish to determine if they potentially qualify to participate in

a clinical trial and who may be interested in seeking additional information about a clinical trial. We noted that our proposed definition of ''eligibility criteria'' was consistent with ''key inclusion and exclusion criteria'' of the WHO Trial Registration Data Set (version 1.2.1) (WHO data item #14) and ICMJE registration policies [Ref. 2, 73] (79 FR 69621). A few commenters addressed the proposed Eligibility Criteria data element. One commenter agreed with the proposal that only ''a limited list of criteria'' be provided but suggested the need for a disclaimer on the posted record that the data element is not intended to represent all eligibility criteria. Although we do not believe that a disclaimer about the eligibility criteria data element on the record is necessary, particularly because there may be cases in which the criteria listed do represent the complete list, we will consider displaying on the public record an explanation that the listed eligibility criteria represent ''key'' or ''selected'' criteria to minimize the potential for confusion. Another commenter suggested requiring the use of standardized terminology for describing the eligibility criteria to facilitate automated, machine-based screening and matching with potential participants. While this is an active area of ongoing research, we are not aware of any widely-accepted data standards for representing eligibility criteria and the commenter did not reference any. Therefore, the final rule does not require the submission of eligibility criteria using any particular standardized terminology, although we encourage responsible parties to submit such information in as structured and standardized a fashion as possible to facilitate data reuse. After considering these comments, we maintain the proposed definition in the final rule. For submission of eligibility criteria information, responsible parties must provide a list of inclusion and exclusion criteria (*e.g.,* Inclusion Criteria: Clinical diagnosis of Alzheimer's Disease, must be able to swallow tablets; Exclusion Criteria: Insulin dependent diabetes, thyroid disease). We note that clinical trial protocols typically contain lengthy, detailed descriptions of inclusion and exclusion requirements for participants, including, for example, specific laboratory test result values. The requirements are often complex and must be assessed by a clinician or researcher involved in the clinical trial. We believe that the submission of all eligibility criteria would be burdensome for responsible parties and, instead of helping prospective participants, would prove confusing or overwhelming to them. We believe that prospective participants are better served by a more limited list of inclusion and exclusion criteria in the data bank to assist in identifying clinical trials of possible interest. Prospective participants who believe they meet the criteria listed in the data bank could discuss the clinical trial with their physician or other healthcare advisor and contact the facility-specific contact or central contact for the clinical trial for more information and a more complete assessment of eligibility. We note that for users of the data bank who want more detailed information about eligibility criteria for the purposes of interpreting clinical trial results information and better understanding the population of human subjects studied, the final rule requires responsible parties to submit protocols as part of the clinical trial results information (see Section III.D. of this preamble).

(B) *Sex/Gender.* In § 11.10(b)(22) of the NPRM, we defined the term ''gender'' to mean, ''the biological sex of the human subjects who may participate in the clinical trial.'' Section 402(j)(2)(A)(ii)(II)(bb) of the PHS Act expressly requires ''gender'' to be submitted as clinical trial information at the time of registration, but it does not define this term. We also proposed that responsible parties would select from the following limited set of choices: ''male,'' ''female,'' or ''both.'' Although no ''other'' option was proposed, the NPRM explained that responsible parties would be able to provide additional, optional free-text information about the gender of participants who may participate in the clinical trial (79 FR 69621).

Several commenters addressed this data element. A few requested that the final rule change the term to ''sex.'' Others stated that use of the term ''sex'' would be consistent with FDA's guidance, ''Evaluation of Sex-Specific Data in Medical Device Clinical Studies,'' in which ''sex'' refers to classification by reproductive organ, and ''gender'' refers to a person's self-representation as male or female [Ref. 95]. They also noted that FDA's guidance is based on an IOM report, ''Exploring the Biological Contributions to Human Health: Does Sex Matter?'' [Ref. 96].

We agree with the commenters that the proposed definition of ''gender'' does not align with the cited definitions and usage of the distinct terms ''gender'' and ''sex.'' The commenters further suggested that we change the data element name from ''Gender'' to ''Sex'' to better align with the proposed definition. Although not mentioned specifically by commenters, we also note that the WHO Trial Registration Data Set (version 1.2.1) describes inclusion and exclusion criteria for participant selection, including age and ''sex.''

To further consider how the terms ''gender'' and ''sex'' are used to define recruitment/eligibility criteria in protocols, we evaluated a convenience sample of 80 study protocols made available online with publication in the Journal of the American Medical Association and the New England Journal of Medicine. Our observations suggest that although protocols use the terms ''gender'' and/or ''sex,'' it was generally not possible to determine whether the usage was appropriate, as definitions of those terms were not typically included. Among the protocols examined, 23 (29 percent) used the term ''gender'' only, 11 (14 percent) used ''sex'' only, 32 (40 percent) appeared to use the terms ''gender'' and ''sex'' interchangeably, and 14 (17 percent) did not use either term. We believe it is important for the information on *ClinicalTrials.gov* to accurately represent the individuals who may participate in the clinical trial, based on information specified in the trial protocol. Based on our evaluation of this sample of protocols and the comments received on the NPRM, we have concluded that the data element needs to be sufficiently flexible to allow responsible parties to submit information about both sex and gender, if those terms are applicable to the trial being registered. We have therefore modified the proposed name of the data element to ''Sex/Gender'' in § 11.28(a)(2)(ii)(B) of the final rule to accommodate studies that base eligibility on sex (meaning, for purposes of this part, a person's classification as male or female based on biological distinctions) and gender (meaning, for purposes of this part, a person's self-representation of gender identity). Similarly, to reflect both terms, we have updated the definition of ''Sex/Gender'' to be ''the sex and, if applicable, gender of the human subjects who may participate in the clinical trial'' in § 11.10(b)(22). The responsible party must indicate the sex of the individuals who may participate in the clinical trial using the following options available on *ClinicalTrials.gov* for this data element: ''male,'' which indicates that only male participants are being studied, ''female,'' which indicates that only female participants are being studied, and ''all'' which indicates that the recruitment

criteria do not limit eligibility based on the sex of participants. In addition, if eligibility for the clinical trial is based on gender, the responsible party may also select from the following options to provide details about gender: ''yes'' (meaning eligibility is based on gender) or ''no'' (meaning eligibility is not based on gender). If the responsible party selects ''yes,'' descriptive information about gender criteria may be provided in the optional, additional, free-text element. Information on gender is required to be submitted only if gender is used as an eligibility/recruitment criterion for the clinical trial. We further note that we consider the Sex/Gender data element complementary to the limited list of criteria submitted as part of the Eligibility Criteria data element, but provision of information on sex/gender in that data element does not substitute for the requirement to provide the Sex/Gender data element.

(C) *Age Limits.* In § 11.10(b)(23) of the NPRM, we defined this term to mean, ''the minimum and maximum age of human subjects who may participate in the clinical trial, provided in relevant units of time.'' Section 402(j)(2)(A)(ii)(II)(cc) of the PHS Act expressly requires ''age limits'' to be submitted as clinical trial information at the time of registration, but it does not define the term (79 FR 69621). We received no comments and therefore retain the proposed data element and definition in the final rule. We clarify, however, that the responsible party selects the unit of time from the following limited set of choices: ''years,'' ''months,'' ''weeks,'' ''days,'' ''hours,'' ''minutes,'' and ''N/A'' (*i.e.,* no limit). These structured choices are consistent with current practice on *ClinicalTrials.gov* and facilitates more specific searches by age limits (*e.g.,* finding studies recruiting children aged 24 to 36 months versus adults aged 24 to 36 years).

(D) *Accepts Healthy Volunteers.* In § 11.10(b)(24) of the NPRM, we defined the Accepts Healthy Volunteers data element to mean ''whether human subjects who do not have a disease or condition, or related conditions or symptoms, under study in the clinical trial are permitted to participate in the clinical trial.'' Section 402(j)(2)(A)(ii)(II)(dd) of the PHS Act requires the submission of information about ''whether the trial accepts healthy volunteers.'' (79 FR 69621) We received no comments and therefore retain the proposed data element and definition in the final rule, except we delete the word ''whether'' in the definition for additional clarity. We note that we consider any human participant in a clinical trial to be a human subject regardless of whether he or she is a healthy volunteer.

(E) *Overall Recruitment Status.* Under § 11.10(b)(25) of the NPRM, we defined the Overall Recruitment Status data element as ''the recruitment status for the clinical trial as a whole, based upon the status of the individual sites. If at least one facility in a multi-site clinical trial has an individual site status of 'recruiting,' then the overall recruitment status for the trial must be 'recruiting.' '' Section 402(j)(2)(A)(ii)(II)(ee) of the PHS Act requires ''overall recruitment status'' to be submitted as clinical trial information at the time of registration, but it does not define the term. To facilitate searching for clinical trials by recruitment status and to allow information to be compared across clinical trials, we also stated in the NPRM that responsible parties would be required to select from the following limited set of choices: ''Not yet recruiting'' (participants are not yet being recruited); ''Recruiting'' (participants are currently being recruited, whether or not any participants have yet been enrolled); ''Enrolling by invitation'' (participants are being, or will be selected from a predetermined population); ''Active, not recruiting'' (study is ongoing, meaning participants are being treated or examined, but new participants are not currently being recruited or enrolled); ''Completed'' (the study has concluded normally; participants are no longer being examined or treated, *i.e.,* last patient's last visit has occurred); ''Suspended'' (recruiting or enrolling participants has halted prematurely but potentially will resume), ''Terminated'' (recruiting or enrolling participants has halted prematurely and will not resume; participants are no longer being examined or treated), and ''Withdrawn'' (study halted prematurely, prior to enrollment of first participant). No ''other'' option was proposed. We invited public comment on whether the proposed options are sufficient to accurately describe the overall recruitment status of clinical trials subject to the proposed rule. We also noted that the proposed definition of ''overall recruitment status'' is consistent with ''recruitment status'' in the WHO Trial Registration Data Set (version 1.2.1) (WHO data item #18) and ICMJE registration policies [Ref. 2, 73] (79 FR 69621).

We received no comments and therefore retain the proposed definition in the final rule. The final rule requires responsible parties to provide and update information for the Overall Recruitment Status data element. Such a requirement will provide users of *ClinicalTrials.gov* with an effective means of tracking the progress of clinical trials, as required by section 402(j)(2)(A)(i) of the PHS Act. However, we clarify the descriptions for the following four choices identified in the NPRM for the Overall Recruitment Status data element: ''Active, not recruiting'' indicates that a ''study is continuing, meaning that participants are receiving an intervention or being examined, but new participants are not currently being recruited or enrolled;'' ''Completed'' indicates that ''the study has concluded normally; participants are no longer receiving an intervention or being examined, *i.e.,* the last patient's last visit has occurred;'' ''Suspended'' indicates that a ''study halted prematurely but potentially will resume;'' and ''Terminated'' indicates that a ''study halted prematurely and will not resume; participants are no longer being examined or receiving an intervention.'' These descriptions are clearer and more accurate for the data element choices. We remove the term ''treated'' from the description of these options and instead use the phrase ''receiving an intervention'' for greater accuracy because not all clinical trials are conducted to evaluate whether interventions are efficacious for the treatment of the disease or condition that is the focus of the study. We note that ''receiving an intervention'' includes receiving a placebo or receiving no intervention, as assigned in the study protocol. The other modifications clarify that the status relates to the entire study, not just the aspect of the study that involves recruitment. We also note that if a clinical trial is registered before it is open to recruitment, we would expect the Overall Recruitment Status to be ''Not yet recruiting.'' When the clinical trial opens for enrollment, we would expect the Overall Recruitment Status to be ''Enrolling by invitation'' if human subjects are selected from a predetermined population or ''Recruiting'' if the study is open to volunteers who meet the study's eligibility criteria. As indicated in the discussion of the Study Start Date data element, for this rule, if a clinical trial is registered prior to enrollment of the first subject and the clinical trial is subsequently halted before the first subject is enrolled, we would expect the responsible party to update the Overall Recruitment Status data element to ''Withdrawn.''

We believe that updating the Overall Recruitment Status data element will provide users of *ClinicalTrials.gov* with

an effective means of tracking the progress of clinical trials, as the data bank is intended to do (see section 402(j)(2)(A)(i) of the PHS Act). In the case of a clinical trial that is halted before the first subject is enrolled (*i.e.,* a status of Withdrawn), this information will explain why no results information can be expected or is required to be submitted. In the case of a clinical trial for which recruitment is prematurely halted (*i.e.,* a status of Suspended or Terminated), this information will allow potential human subjects to determine whether enrollment is likely to resume. Such information will also assist in the interpretation of results information, for example, by providing an explanation of why some clinical trial outcomes were not achieved and/or enrollment was significantly below the target. We note that when a study has reached its study completion date, as defined in § 11.10(a), the Overall Recruitment Status would be Completed, unless the responsible party terminates the study, which would be reflected in a status of Terminated.

(F) *Why Study Stopped.* Proposed § 11.10(b)(26) of the NPRM defined the Why Study Stopped? data element to mean ''for a clinical trial that is suspended or terminated or withdrawn prior to its completion as anticipated by the protocol, a brief explanation of the reason(s) why such clinical trial was stopped.'' We proposed allowing responsible parties to enter this information as a free-text response, to provide them with the flexibility to explain the reason(s) why a clinical trial stopped prematurely. While this information is not required for submission by section 402(j) of the PHS Act, we indicated that it is important to communicate to users of the data bank why a clinical trial was suspended, terminated, or withdrawn (*e.g.,* safety concerns, difficulties in recruitment, financial reasons). Such information also furthers the statutory objective stated in section 402(j)(2)(A)(i) of the PHS Act to enable users ''to track subsequent progress of clinical trials.'' As we stated in the NPRM, for these reasons requiring this information improves and does not reduce the clinical trial information available in the data bank, consistent with the authority granted to the Agency under section 402(j)(2)(A)(iii) of the PHS Act. We also indicated our concern that if such information were not required in each instance in which a clinical trial is stopped prematurely (*i.e.,* not according to the protocol), it might be submitted only for some trials, resulting in inconsistencies in the information available for registered clinical trials (79 FR 69622).

Two commenters requested that for this data element the final rule require only the submission of reasons for stopping a study that are directly related to safety. These commenters asserted that any other reasons would be business reasons, which would be confidential commercial information prohibited from disclosure. As we explained in the NPRM, we believe it is important for responsible parties to provide any reasons for stopping a study, whether or not they relate to safety. This increased transparency will assist the public, including patients, in understanding the reasons why a trial was stopped. We also note that this proposed definition specifies that any explanation provided be brief; therefore, we do not believe that a responsible party will need to provide any confidential commercial or proprietary information when submitting the information for this data element. However, even if the summary results information required to be submitted and posted does include such proprietary information, as discussed above, section 402(j) of the PHS Act and this final rule constitute authorization by law to disclose the information.

After considering the comments, we are maintaining the NPRM definition in the final rule. We note that §§ 11.10(b)(26) and 11.64(a)(1) specify that a brief explanation for why the clinical trial was stopped must be submitted if the Overall Recruitment Status is ''Suspended,'' ''Terminated,'' or ''Withdrawn.'' In most cases, the Overall Recruitment Status of a clinical trial would be other than Suspended, Terminated, or Withdrawn at the time of registration (*e.g.,* a status of ''Not yet recruiting'' or ''Recruiting''). The responsible party would not be required to complete the Why Study Stopped data element unless and until there is a change in the Overall Recruitment Status to Suspended, Terminated, or Withdrawn. (The Why Study Stopped data element would not be available to a responsible party during the registration process nor to the public in the posted clinical trial record, unless and until the Overall Recruitment Status indicates that the clinical trial is Suspended, Terminated, or Withdrawn.) However, if a clinical trial is suspended, terminated, or withdrawn, the responsible party would be required to update the Overall Recruitment Status data element and, consistent with § 11.64(a)(1), submit the Why Study Stopped data element not later than 30 calendar days after the date of the suspension, termination, or withdrawal of the clinical trial to explain why the study stopped.

(G) *Individual Site Status.* In proposed § 11.10(b)(28) of the NPRM, we defined this data element as ''the recruitment status of each participating facility in a clinical trial.'' Section 402(j)(2)(A)(ii)(II)(ff) of the PHS Act expressly requires ''individual site status'' to be submitted as a clinical trial information at the time of registration, but it does not define the term. To be consistent with the proposed Overall Recruitment Status data element, we also stated in the NPRM that responsible parties would be required to indicate the individual site status by selecting from the following limited set of choices: ''Not yet recruiting,'' ''Recruiting,'' ''Enrolling by invitation,'' ''Active, not recruiting,'' ''Completed,'' ''Suspended,'' ''Terminated,'' and ''Withdrawn.'' No ''other'' option was proposed. We invited public comment on whether the proposed options were sufficient to accurately describe the individual site status of clinical trials that would be subject to the proposed rule (79 FR 69623). Two commenters suggested that the final rule remove the proposed requirement for registering and updating the Individual Site Status data element for each participating facility in the trial. The Individual Site Status data element is required by section 402(j)(2)(A)(ii)(II)(ff) of the PHS Act. Furthermore, such information supports the purpose of *ClinicalTrials.gov* to enhance patient enrollment by assisting potential human subjects who search for clinical trials by location and wish to retrieve information about only those trials that are open to recruitment in specified locations. We clarify that when the Overall Recruitment Status is a status other than Recruiting, the Individual Site Status data element no longer needs to be updated because the Overall Recruitment Status would apply to each individual site. We also note that the update burden for responsible parties is reduced by tools available in the PRS that allow the Individual Site Status data element to be easily changed (*e.g.,* from Recruiting to Active, not recruiting) for many sites at once. After considering the comments, we retain the proposed definition in the final rule. However, we clarify these descriptions as described for the Overall Recruitment Status data element. Specifically, we modify the following four choices for the Individual Site Status data element from the limited set described in the NPRM: ''Active, not recruiting'' indicates that a study is continuing, meaning that participants are receiving

an intervention or being examined, but new participants are not currently being recruited or enrolled; ''Completed'' indicates that the study has concluded normally and that participants are no longer receiving an intervention or being examined, *i.e.,* the last patient's last visit has occurred; ''Suspended'' indicates that a study halted prematurely but potentially will resume; and ''Terminated'' indicates that a study halted prematurely and will not resume and that participants are no longer being examined or receiving an intervention. We note that when a study has reached its study completion date, as defined in § 11.10(a), the Individual Site Status would be Completed, unless the responsible party terminates the study, which would be reflected as a status of Terminated.

(H) *Availability of Expanded Access.* Section 402(j)(2)(A)(ii)(II)(gg) of the PHS Act specifies that if a drug (including a biological product) being studied in an applicable clinical trial is not approved under section 505 of the FD&C Act or licensed under section 351 of the PHS Act, the responsible party must specify (1) ''whether or not there is expanded access to the drug under section 561 of the [FD&C Act] for those who do not qualify for enrollment in the clinical trial'' and, if so, (2) ''how to obtain information about such access.'' As we expressed in the NPRM, we believe the purpose of this requirement is to allow prospective human subjects and other users of the data bank to readily identify unapproved drugs that are available through expanded access under section 561 of the FD&C Act and to direct these users to additional information about the expanded access. Therefore, we proposed that responsible parties meet the requirements of section 402(j)(2)(A)(ii)(II)(gg) of the PHS Act by indicating in the clinical trial record whether expanded access is available for the drug under study (*i.e.,* either ''yes'' or ''no'') and, if yes, submitting the additional information about the expanded access in the form of an expanded access record under proposed § 11.28(c) and including the NCT number for the expanded access record in the record of a clinical trial that studies the drug.

In the NPRM, we proposed to require the submission of information to create an expanded access record using the statutory authority at section 402(j)(2)(A)(iii) of the PHS Act, which allows the Secretary by regulation to modify the requirements for clinical trial registration information if the Secretary provides a rationale for why such a modification ''improves and does not reduce such clinical trial information.'' Information about the availability of expanded access would be a data element that a responsible party is required to submit under section 402(j)(2)(A)(ii)(II) of the PHS Act and, therefore, would meet the definition of ''clinical trial information'' in section 402(j)(1)(A)(iv) of the PHS Act. We indicated that the additional data elements describing expanded access availability would improve, and not reduce, this clinical trial information by providing users with more complete and consistent information about expanded access programs for drugs studied in applicable clinical trials than would be available pursuant to section 402(j)(A)(ii)(II)(gg) of the PHS Act alone. We further concluded that we have the authority to require that the clinical trial information required under proposed § 11.28(c) be submitted by creating a separate expanded access record in *ClinicalTrials.gov* under section 402(j)(2)(B)(iv) of the PHS Act, as the expanded access record would ensure that the public may more easily use the data bank to determine whether there is expanded access to a drug and compare different expanded access programs.

The approach we proposed is similar to the one used to submit a description of whether, and through what procedure, the manufacturer or sponsor will respond to requests for protocol exception, with appropriate safeguards, for single-patient and expanded access use of the investigational drug, particularly in children, prior to the enactment of FDAAA [Ref. 78, 79]. Proposed § 11.28(a)(2)(ix) would require the responsible party for an applicable clinical trial of a drug that is not approved under section 505 of the FD&C Act to submit the Availability of Expanded Access data element, which was defined in proposed § 11.10(b)(29) to include ''[a]n indication of whether there is expanded access to the drug under section 561 of the [FD&C Act] (21 U.S.C. 360bbb) for those who do not qualify for enrollment in the applicable clinical trial,'' and, if expanded access is available, ''the NCT number of the expanded access record.'' The availability of expanded access would be indicated by a yes/no designation in *ClinicalTrials.gov*. In addition, if the drug studied in the clinical trial is available through expanded access under section 561 of the FD&C Act and an expanded access record has not been created, under the NPRM the responsible party would be required to create an expanded access record consisting of the information specified in proposed § 11.28(c). The posted expanded access record would be assigned its own NCT number and thus would be searchable and retrievable independent of the record(s) for the applicable clinical trial(s) of the investigational product for which expanded access is available.

Under the proposed approach, we stated that we would expect the sponsor of the expanded access program to be responsible for (1) informing the responsible party(ies) for any applicable clinical trials that study the drug available under expanded access of the creation of an expanded access record and (2) providing them with the NCT number for the expanded access record. The responsible party(ies) would be required to update the related clinical trial record under proposed § 11.64(b) to include the NCT number for the expanded access record within 30 calendar days of receipt. Accordingly, a single expanded access record could be linked, via the expanded access record NCT number, to several applicable clinical trials that study the drug that is available via expanded access. If an expanded access record has already been completed at the time of registration of an applicable clinical trial (*e.g.,* to fulfill the registration or updating requirements for a previously registered applicable clinical trial), the responsible party would be required to submit the NCT number for that expanded access record as part of the Availability of Expanded Access data element. The NPRM also noted that expanded access is available via treatment INDs, which provide widespread access; expanded access for intermediate-size patient populations; and expanded access for individual patients (79 FR 69624). As we stated in the NPRM, because requests for individual patient access are generally handled on a case-by-case basis, a responsible party likely would not be able to provide detailed information describing individual patient access at the time of registering an applicable clinical trial. For cases in which expanded access is only available for individual patients on a case-by-case basis, we stated that we would not require the responsible party to submit the elements of the expanded access record, as described below, and we would expect that users of *ClinicalTrials.gov* would direct inquiries regarding individual patient access to the facility contact.

Commenters addressed issues related to the Availability of Expanded Access data element in proposed § 11.28(a)(2)(ix) and its definition in proposed § 11.10(b)(29). A few commenters expressed support for the

proposed data element and its definition. A few commenters supported, in particular, the proposed requirement that responsible parties for applicable clinical trials of drugs available through expanded access provide the NCT number for the expanded access record to permit linking from clinical trial records to additional information about the expanded access program. One commenter opposed the proposed requirement for creating expanded access records because of concerns that such records may (1) mislead patients into believing that no other opportunities to obtain expanded access exist beyond what is described in expanded access records because the proposal does not require the submission of information about individual patient access and/or (2) confuse patients regarding the distinction between clinical trials and expanded access programs. We agree with the commenter that requiring the submission of registration information for only certain types of available expanded access programs, as proposed, could be problematic. In addition, section 402(j)(2)(A)(ii)(II)(gg) of the PHS Act broadly requires ''specify[ing] whether or not there is expanded access to the drug under section 561 of the Federal Food, Drug, and Cosmetic Act'' and does not explicitly exclude individual patient expanded access.

After considering these comments and the statutory provision, in the final rule we have revised the requirements regarding the information to be submitted about the availability of expanded access to investigational drug products (including biological products). We have also clarified that ''drug'' means ''drug product.'' Therefore, under the final rule, if an investigational drug product (including a biological product) is available for any type of expanded access, and the responsible party for an applicable clinical trial of that product is both the manufacturer of the product and the sponsor of the applicable clinical trial, the responsible party must create an expanded access record for the investigational product by submitting the expanded access data elements specified in § 11.28(c) of the final rule. We note that only one expanded access record should be created for any given investigational product, even if the investigational product is being made available for individual patient expanded access (*i.e.,* the responsible party should not create an expanded access record for each instance of individual patient access). This approach permits users of *ClinicalTrials.gov* to identify the full range of expanded access availability under section 561 of the FD&C Act by searching posted expanded access records.

Another commenter requested that posted clinical trial records be made ''separate and distinct'' from expanded access records to avoid confusion and suggested that *ClinicalTrials.gov* provide sponsors with the ability to link to their expanded access policy and contact Web pages. We recognize the potential for confusion between expanded access records and clinical trial records and have sought to help users distinguish between them (*e.g.,* prominently displaying Study Type of ''Expanded Access'' versus ''Interventional Study,'' and Overall Recruitment Status displayed as ''Expanded access is currently available for this treatment'' versus ''This study is currently recruiting participants''). We will continue to explore ways to differentiate between the two types of records. With regard to the second comment, we note that *ClinicalTrials.gov* currently permits responsible parties to submit URLs of Web sites through the optional Links data element.

One commenter requested that the final rule define ''expanded access program'' and clarify for which expanded access programs the data elements specified in proposed § 11.28(c) would be required under the final rule. In particular, although the preamble of the NPRM stated that responsible parties would not be required to create expanded access records when expanded access is available only through individual patient access, this distinction was not specified in the codified section of the NPRM. The commenter suggested that the final rule state explicitly which types of expanded access programs require the creation of expanded access records, such as by adding a definition of expanded access in § 11.10 of the final rule. Another commenter suggested that the final rule narrow the proposed definition of Availability of Expanded Access to section 561(c) of the FD&C Act, thereby limiting the types of expanded access programs ''to intermediate-size and large-size treatment INDs with established inclusion/exclusion enrollment parameters and exclude[ing] emergency situations and individual patient access to INDs intended for serious diseases.''

We agree that the codified section of the proposed rule did not provide specificity with respect to the term ''expanded access program.'' After considering the issue, in the final rule, we have revised the phrase ''expanded access program'' to ''expanded access'' for an expanded access record to more accurately characterize the mechanism through which a responsible party makes its investigational product available under expanded access. This flexibility will accommodate both situations in which a responsible party has established what it considers to be an expanded access program and those in which a responsible party makes its investigational product available through expanded access but does not itself characterize that availability as a ''program.'' Furthermore, because the statutory requirement for providing information about expanded access did not explicitly exclude individual patient expanded access, we disagree with the commenter that *ClinicalTrials.gov* should only include information on certain types of expanded access. The final rule broadens the scope of the proposed rule to include and define all three types of expanded access under section 561 of the FD&C Act: (1) For individual patients, including emergency use, as specified in 21 CFR 312.310; (2) for intermediate-size patient populations as specified in 21 CFR 312.315; and (3) under a treatment IND or treatment protocol as specified in 21 CFR 312.320. Section 11.10(b)(28) of the final rule, which defines the Availability of Expanded Access data element, clarifies that if the investigational product is available for any of these three types of expanded access, the NCT number of a corresponding expanded access record must be submitted. As such, the definition of and requirements for the Availability of Expanded Access data element in the final rule cover all types of expanded access for investigational drug products (including biological products) under section 561 of the FD&C Act, consistent with the statutory requirements. Additionally, § 11.28(c) of the final rule, which indicates the data elements that must be submitted for an expanded access record, lists the Expanded Access Type data element, which is defined as ''[t]he type(s) of expanded access for which the investigational drug product is available, as specified in § 11.10(b)(28).''

A few commenters expressed concern that requiring responsible parties who are not industry sponsors and manufacturers of the drug to create expanded access records could be problematic because only a manufacturer would know when expanded access to a drug becomes available and would possess the

information required to be submitted under § 11.28(c) and updated under § 11.64. Accordingly, they suggested that the final rule only require responsible parties who are industry sponsors of relevant trials and manufacturers of the drug to create expanded access records for their drugs. Several commenters suggested that the final rule require drug manufacturers to notify responsible parties for applicable clinical trials when drugs become available through expanded access programs and that *ClinicalTrials.gov* could notify responsible parties who are not drug manufacturers when an expanded access record has been submitted for the drug being studied in their applicable clinical trials. They also requested guidance on whether the Agency would recommend that ''investigators of investigator-initiated trials'' seek agreements from manufacturers that require notification that an expanded access program for a studied drug becomes available. One other commenter requested clarification on two issues: (1) How independent investigators who are responsible parties for applicable clinical trials would know when and what information to submit for an expanded access record when the manufacturer makes a drug they are studying available through expanded access and (2) whether the proposed rule intended for the manufacturer to provide one expanded access record per drug and an indication for the purposes of the registration requirements.

We agree with the concerns raised by these commenters and have modified the final rule to specify that the requirement to submit information for the Availability of Expanded Access data element only applies to a responsible party who is both the manufacturer of the investigational drug product (including a biological product) and the sponsor of the applicable clinical trial for that investigational product. We believe that these new requirements will decrease the burden on responsible parties who are not the manufacturer without impeding access to information posted on *ClinicalTrials.gov* about the availability of investigational drug products (including biological products) for expanded access. At the same time, these new requirements will ensure that only one expanded access record is created for each investigational drug product that is available for expanded access for any disease or condition. We wish to emphasize, however, that an expanded access record is required to be submitted regardless of whether the responsible party registering the applicable clinical trial, who is both the sponsor of the applicable clinical trial and the manufacturer of the investigational product, itself oversees the availability of the investigational product for expanded access (*i.e.,* it is required even in situations where the expanded access availability is managed by a different entity). If certain data elements required for submitting an expanded access record under § 11.28(c) are unknown to the responsible party because the expanded access availability is managed by a different entity, the responsible party will need to consult with NIH concerning these data elements before submitting the expanded access record. Instructions for contacting NIH will be available at *https://prsinfo.clinicaltrials.gov* (or successor site).

In addition, responsible parties will no longer need to be notified by the manufacturer when an investigational drug product (including a biological product) is available through expanded access. We note that there may be cases in which the sponsor who is the manufacturer of the unapproved drug product (including a biological product) may designate the principal investigator to be the responsible party of an applicable clinical trial of that product. Based on our experience operating *ClinicalTrials.gov*, we expect the designation of a principal investigator to be the responsible party by a manufacturer to be a rare event. If it does occur, we recommend that the sponsor provide the necessary information to the responsible party or, on an optional basis, create an expanded access record to allow information about expanded access to be shared with individuals who do not qualify for enrollment in the clinical trial.

One commenter suggested that *ClinicalTrials.gov* provide links between applicable drug clinical trial records and expanded access records for the studied drugs and provide appropriate caveats about the expanded access programs. *ClinicalTrials.gov* is able to provide the appropriate links between matched clinical trial records and expanded access records after a responsible party has identified in the clinical trial record(s) that the investigational drug product (including a biological product) is available through a particular expanded access program. Once the responsible party submits the NCT number for the relevant expanded access record, *ClinicalTrials.gov* creates and displays a link on the clinical trial record to the related record for the expanded access program. We can also provide links from expanded access records to the matched clinical trial records. We note that *ClinicalTrials.gov* currently provides links to information about expanded access on FDA's Web site (*e.g., www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm*). As suggested by the commenter, we will consider providing additional information about expanded access or links on *ClinicalTrials.gov.*

Taking into consideration the commenters' suggestions and the statutory requirements for providing information about expanded access as part of clinical trial registration information, § 11.28(a)(2)(ii)(H) of the final rule modifies the Availability of Expanded Access data element with respect to which responsible parties must submit the data element and by expanding the submission requirement to include applicable clinical trials for which the investigational drug products (including biological products) that are being studied are available through individual patient expanded access, including for emergency use. The Availability of Expanded Access data element as defined in § 11.10(b)(28) and specified in § 11.28(a)(2)(ii)(H) of the final rule indicates whether the unapproved drug product (including a biological product) studied in the applicable clinical trial is available for expanded access under section 561 of the FD&C Act for those who do not qualify for enrollment in the applicable clinical trial (*i.e.,* ''yes,'' ''no,'' or ''unknown''). Under the final rule, the requirement to submit the data element is limited to a responsible party for an applicable clinical trial of an unapproved drug product (including a biological product) who is both the manufacturer of the drug product and the sponsor of the trial. Therefore, a responsible party for an applicable drug clinical trial who is not the manufacturer of the drug product (including a biological product) would not be required to submit information for the Availability of Expanded Access data element (*i.e.,* response of ''unknown''). This modification will decrease the burden on responsible parties who are not the manufacturer but will still help ensure the availability of information about expanded access on *ClinicalTrials.gov.*

For an investigational drug product (including a biological product) that is available through expanded access, including for individual patients, the responsible party who is both the manufacturer of the investigational drug product (including biological product) and the sponsor of an applicable clinical

trial must provide the NCT number of the expanded access record as part of the clinical trial information for that applicable clinical trial. If an expanded access record for the investigational drug product (including a biological product) has not yet been submitted to *ClinicalTrials.gov,* the responsible party is required to create an expanded access record as specified in § 11.28(c). This new requirement will provide users of *ClinicalTrials.gov* with a way to obtain information about available expanded access to an investigational drug product (including a biological product) as required by the statute, including for individual patients.

We note that even though the expanded access record NCT number is a registration data element, a responsible party is not required to submit the expanded access data elements under § 11.28(c) and obtain an NCT number for that expanded access record prior to the date on which clinical trial registration information under § 11.28(a) is due for the first applicable clinical trial of that investigational product that the responsible party registers. Rather, the responsible party is required at the time it submits clinical trial registration information for the applicable clinical trial to indicate that expanded access is available, submit the applicable data elements required by § 11.28(c), and indicate that the NCT number for the expanded access record is ''pending.'' As described previously, within 30 calendar days of receipt of the NCT number for the expanded access record, the responsible party is required to update the applicable clinical trial record with the NCT number assigned to the expanded access record. Finally, we note both that expanded access to an investigational drug product (including a biological product) may not be available at the time an applicable clinical trial is registered and that an expanded access program may be discontinued on a date other than the study completion date of an applicable clinical trial. We believe that information about changes in the availability of expanded access must be conveyed to users of *ClinicalTrials.gov* in a timely manner and therefore Availability of Expanded Access is a data element that must be updated more frequently than once every 12 months. Accordingly, as explained in further detail in § 11.64, the Availability of Expanded Access data element must be updated within 30 calendar days of expanded access becoming available, consistent with § 11.64(a).

(iii) Location and Contact Information

(A) *Name of the Sponsor.* In § 11.10(b)(30) of the NPRM, Name of the Sponsor is defined as ''the name of the entity or the individual that is the sponsor of the clinical trial, as defined in § 11.10(a).'' Section 402(j)(2)(A)(ii)(III)(aa) of the PHS Act expressly requires responsible parties to submit the name of the sponsor as part of clinical trial information at the time of registration. In the NPRM, the term ''sponsor'' is defined as ''either a 'sponsor' or 'sponsor-investigator,' as each is defined in 21 CFR 50.3, or any successor regulation.'' As we indicated, if the sponsor is a sponsor-investigator, we would expect the name of the sponsor to be the name of an individual; otherwise the name of the sponsor may be an organizational name (79 FR 69624). We received no comments on this data element and therefore retain the proposed definition in the final rule, however, we made minor grammatical corrections (*e.g.,* changing ''that'' to ''who'').

(B) *Responsible Party, by Official Title.* Section 11.10(b)(31) of the NPRM defined Responsible Party, by Official Title to mean ''(i) Indication of whether the responsible party is the sponsor of the clinical trial, as that term is defined in 21 CFR 50.3, the sponsor-investigator, as that term is defined in 21 CFR 50.3, or a principal investigator designated pursuant to this part; and (ii) Either: (A) The official name of the entity, if the responsible party is an entity; or (B) The official title and primary organizational affiliation of the individual, if the responsible party is an individual.'' Section 402(j)(2)(A)(ii)(III)(bb) of the PHS Act expressly requires the submission of the ''responsible party, by official title'' as part of clinical trial registration information. When an organizational entity is the responsible party, we noted our belief that the official name of the entity (*e.g.,* company name, university name, government agency name) must be included to satisfy the requirement for the Responsible Party, by Official Title data element. When the responsible party is an individual, we noted our belief that the official job title and the organizational affiliation of the individual are necessary (*e.g.,* ''Director of Clinical Research, Institution X'' or ''Professor of Medicine, Institution Y''). In addition, we indicated that we believe it is necessary to ask whether the responsible party is the sponsor, sponsor-investigator, or a principal investigator designated by the sponsor, grantee, contractor, or awardee. Collection of this information will help determine what information must be provided for the official title and will allow a principal investigator to provide an affirmative acknowledgement that he or she has been designated the responsible party (79 FR 69624). We received no comments on this data element and therefore retain the proposed definition in the final rule. We note that an individual who serves as a responsible party and has multiple affiliations (*e.g.,* a research university and a teaching hospital, a research institution and a private company) would be required to submit only one such affiliation, namely, the affiliation that the individual considers their primary affiliation. A related data element, Responsible Party Contact Information, is defined in § 11.10(b)(37).

(C) *Facility Information.* In § 11.10(b)(32) of the NPRM, we defined Facility Information as (1) ''Facility Name, meaning the full name of the organization where the clinical trial is being conducted''; (2) ''Facility Location, including city, state, country and zip code for U.S. locations (including territories of the United States) and city and country for locations in other countries,'' and (3) for each participating facility either ''a Facility Contact, including the name or title, telephone number, and email address of a person to whom questions concerning the trial and enrollment at that site can be addressed'' or a ''Central Contact Person, including the name or title, toll-free telephone number and email address of a person to whom questions concerning enrollment at any location of the trial can be addressed.'' Section 402(j)(2)(A)(ii)(III)(cc) of the PHS Act expressly requires the submission of ''the facility name and facility contact information'' as part of clinical trial information at the time of registration and describes facility contact information as ''including the city, State, and zip code for each clinical trial location, or a toll-free number through which such location information may be accessed.'' Section 402(j)(2)(B)(i) of the PHS Act requires the Director to ensure that the public may search the entries in *ClinicalTrials.gov* by one or more of several enumerated criteria, one of which is ''location of the clinical trial.'' In the NPRM, we interpreted ''location of the clinical trial'' to mean each location of the clinical trial because section 402(j)(2)(A)(ii)(III)(cc) of the PHS Act describes ''facility contact information'' as meaning contact information ''for each clinical trial location.'' To enable the public to search the data bank by the location of the

clinical trial; in our view, satisfactory searching of the data bank by location can only be accomplished if responsible parties submit complete facility location information for each clinical trial location. Also, in our view, a toll-free telephone number is not a substitute for the location information for each facility or site but rather is a source of supplementary information about the clinical trial overall and an alternative to site-specific contact information for each location. Therefore, the Agency proposed to exercise its authority under section 402(j)(2)(A)(iii) of the PHS Act as we noted our belief that including this information improves and does not reduce the clinical trial registration information. We noted that our proposal to permit responsible parties to submit Central Contact instead of Facility Contact was intended to reduce the burden on responsible parties who must submit clinical trial registration information. However, the central contact person should be fully informed of, and able to respond to, requests for information concerning the clinical trial at all of its sites (79 FR 69625).

Commenters addressed the proposed Facility Information data element. One commenter requested that facilities located outside of the United States be excluded from the submission requirements. We disagree with this comment. As discussed in the preamble of the NPRM, we interpret ''location of the clinical trial'' in this context as meaning each location of the clinical trial because section 402(j)(2)(A)(ii)(III)(cc) of the PHS Act describes ''facility contact information'' as meaning contact information ''for each clinical trial location.'' Because the final rule is not limited to applicable clinical trials that are conducted in the United States, and because it is important that the database be complete in order to allow users to search for registered trials by key characteristics (including where they are being conducted), the Facility Information data element must include information about all facility locations, including those outside the United States. A few commenters suggested that the final rule limit the required Facility Contact Information sub-element to information about the facility, rather than also requiring information about an individual, as proposed. One commenter suggested requiring only a toll-free telephone number for the Central Contact Person and removing the proposed requirement for a name or title and an email address to reduce the reporting burden and the submission of personally identifiable information. Another commenter suggested that providing contact information for each facility participating in a trial would increase the burden on academic sites to respond to inquiries and requested confirmation that a toll-free phone number is only required for the Central Contact Person, if provided, and not for each study facility. One commenter suggested that the final rule clarify that the proposed Central Contact Person sub-element defined in § 11.10(b)(32)(iii)(B) applies to the entire trial. Another commenter supported the inclusion of contact information for someone who is knowledgeable about the trial at each facility.

We disagree with these comments and maintain the definition of ''Facility Information.'' As explained in the preamble of the NPRM, the requirement that the responsible party must submit to the data bank the location of each facility at which the clinical trial is conducted will allow users of *ClinicalTrials.gov* to search the data bank by each clinical trial location (79 FR 69625). We believe that providing ''the name or title . . . of a person to whom questions concerning the trial and enrollment at that site can be addressed . . .'' helps users identify who they can contact for additional information about a trial. In addition, we believe that a toll-free telephone number is not a substitute for the location information for each facility, but rather is a source of supplementary information about the clinical trial overall and an alternative to site-specific contact information for each location. Because a toll-free phone number in one country may not be applicable when a call originates in another country, and given the worldwide prevalence of electronic communication, we believe that submitting email addresses is necessary to provide an alternate method of contacting someone knowledgeable about the trial. Finally, we note that proposed § 11.10(b)(32)(iii)(B) already specified ''a person to whom questions concerning enrollment at any location of the trial can be addressed'' and we believe that this description sufficiently indicates that the person must be knowledgeable about all the locations for a trial.

For these reasons, we believe including the information required in the final rule improves and does not reduce the clinical trial registration information. Under our authority in section 402(j)(2)(A)(iii) of the PHS Act, we therefore modify in § 11.28(a)(2)(iii)(C) the requirement in section 402(j)(2)(A)(ii)(III)(cc) of the PHS Act for ''facility name and facility contact information'' to require Facility Information for each participating facility in the clinical trial, as defined in § 11.10(b)(31). As noted above, the Agency intends to exercise its authority under section 402(j)(2)(B)(i) of the PHS Act to enable the public to search the data bank by the location of a clinical trial; in our view, satisfactory searching by location can only be accomplished if responsible parties submit complete facility location information for each clinical trial location. In addition, the final rule allows, but does not require, responsible parties to submit the name or title of a person knowledgeable about the clinical trial at each site, along with the phone number and email address of that person, which would help prospective human subjects obtain additional, specific information about a clinical trial at a particular location. Responsible parties will also be permitted to submit a Central Contact Person instead of Facility Contact, which will reduce the burden on responsible parties who must submit clinical trial registration information. As noted in the NPRM preamble, the central contact person should be fully informed of, and able to respond to, requests for information concerning the clinical trial for all its sites (79 FR 69625).

(iv) Administrative Data

Section 402(j)(2)(A)(ii)(IV) of the PHS Act provides for certain ''administrative data'' to be submitted by responsible parties as part of clinical trial registration information; however, unlike the other categories of clinical trial registration information, the statute specifies that the Secretary may make administrative data ''publicly available as necessary.'' Accordingly, in the NPRM, we indicated whether we would make the information publicly available through *ClinicalTrials.gov*.

(A) *Unique Protocol Identification Number.* In § 11.10(b)(33) of the NPRM, we defined ''unique protocol identification number'' to mean ''any unique identification number assigned to the protocol by the sponsor.'' Section 402(j)(2)(A)(ii)(IV)(aa) of the PHS Act expressly requires the submission of ''the unique protocol identification number'' as part of clinical trial information at the time of registration, but it does not define the term (79 FR 69625). We did not receive any comments on this data element, but we are modifying the proposed data element in the final rule for accuracy. To clarify that the unique protocol identifier need not be a number, Unique Protocol Identification Number is defined in the final rule as ''any unique identifier assigned to the protocol by the

sponsor.'' We note that once a unique protocol identifier is entered on *ClinicalTrials.gov,* the same identifier cannot be assigned to another protocol for another clinical trial in the sponsor's *ClinicalTrials.gov* account. In cases in which multiple identifiers may have been assigned to a clinical trial (*e.g.,* a funding organization's grant number, a unique identifier established by another clinical trial registry), interpreting this term as an identifier ''assigned by the sponsor'' will remove any ambiguity for responsible parties about which identifier to submit as the unique protocol identifier for purposes of registration on *ClinicalTrials.gov.* We also expect that the unique protocol identifier would be readily available to the responsible party, whether the sponsor or a designated principal investigator who would have access to the protocol itself and/or be able to obtain the unique protocol identifier from the sponsor. Furthermore, these identifiers are often used in other clinical trial documentation, which will enable cross-referencing of information submitted to different data systems. To enable such cross-referencing, this data element will be publicly available on *ClinicalTrials.gov.*

(B) *Secondary ID.* In § 11.10(b)(34) of the NPRM, we defined the term, in part, as ''[a]ny identification number(s) other than the organization's unique protocol identification number or NCT number that is assigned to the clinical trial . . .'' Section 402(j)(2)(A)(ii)(IV)(bb) of the PHS Act expressly requires the submission of ''other protocol identification numbers, if any,'' at the time of registration, but it does not define the term. We also proposed that the Secondary ID include the complete grant or contract number for any clinical trial that is funded, in whole or in part, by a U.S. Federal Government agency and ''any unique clinical trial identification numbers assigned by other publicly available clinical trial registries'' (*e.g.,* EudraCT in the EU). This requirement would enable users of *ClinicalTrials.gov* to identify Government-funded clinical trials. It also would assist agencies of the Department (including NIH, FDA, the Centers for Disease Control and Prevention, and the Agency for Healthcare Research and Quality) to verify that clinical trial information for each applicable clinical trial for which a grantee is the responsible party has been submitted consistent with sections 402(j)(2) and (3) of the PHS Act and this part before the agency releases any remaining funding for a grant or provides funding for a future grant to such grantee as required under section 402(j)(5)(A)(ii) of the PHS Act of any agency of the Department that funds applicable clinical trials. In addition, the inclusion of grant and contract numbers for awards from other federal agencies (*e.g.,* Department of Veterans Affairs, Department of Defense) would facilitate efforts by the Secretary, as required under section 402(j)(5)(A)(iv) of the PHS Act, to consult with such other agencies and develop comparable procedures for the verification of compliance with the requirements of sections 402(j)(2) and (3) of the PHS Act. Finally, in order for users to interpret the various types of secondary ID information that might be provided in response to this requirement, we proposed to require responsible parties to submit ''[a] description of the type of Secondary ID'' for each secondary ID submitted. We stated that these descriptions should be brief but should clearly indicate the source of the identifier, *e.g.,* ''U.S. NIH Grant Number'' or ''[XYZ] Registry Identifier.'' To facilitate data entry and improve comparability across registered clinical trials, we stated that we would include a list of several common identifier types in *ClinicalTrials.gov,* as well as permitting free-text entriesl (79 FR 69626).

Currently, *ClinicalTrials.gov* allows responsible parties to select from the following options: ''US NIH Grant/Contract Award Number,'' ''Other Grant/Funding Number,'' ''Registry Identifier,'' ''EudraCT Number,'' and ''Other Identifier.'' Responsible parties who select ''Other Grant/Funding Number,'' ''Registry Identifier,'' or ''Other Identifier'' are required to enter the name of the funding organization or a brief description of the identifier. One commenter supported the proposal to require responsible parties to provide the complete grant or contract number for any trial that is funded in whole or part by a U.S. Federal Government agency. We modify the proposed data element in the final rule for accuracy in a manner similar to the modifications made to the Unique Protocol Identification Number. To clarify that a secondary identifier need not be a number, Secondary ID is defined in the final rule, in part, as ''[a]ny identifier(s) other than the organization's unique protocol identifier or NCT number that is assigned to the clinical trial, including any unique clinical trial identifiers assigned by other publicly available clinical trial registries.'' We will post the secondary ID publicly, as this information will enable users to locate additional information in other clinical trial registries as well as provide grant and contract numbers for awards from other Federal agencies.

(C) *U.S. Food and Drug Administration IND or IDE Number.* In § 11.10(b)(35) of the NPRM, we defined the Food and Drug Administration IND or IDE Number data element to include an indication whether or not there is an IND or IDE for the clinical trial (a yes/no response) and, if so, each of the following elements: (1) ''[n]ame or abbreviation of the FDA center with whom the IND or IDE is filed''; (2) ''IND or IDE number assigned by the FDA center''; and (3) for an IND, ''the IND serial number (as defined in 21 CFR 312.23(c), or any successor regulation), if any, assigned to the clinical trial.'' Section 402(j)(2)(A)(ii)(IV)(cc) of the PHS Act expressly requires the ''Food and Drug Administration IND/IDE protocol number'' to be submitted to *ClinicalTrials.gov* at the time of registration in *ClinicalTrials.gov,* but it does not define this term. FDA does not issue an ''IND/IDE protocol number,'' as referred to in section 402(j)(2)(A)(ii)(IV)(cc) of the PHS Act; rather it issues an IND or IDE number. We therefore proposed to use the term ''Food and Drug Administration IND or IDE number'' to identify this data element on *ClinicalTrials.gov.* We also recognized that not all applicable clinical trials will be conducted under an IND or IDE (*e.g.,* because they are exempt). Because Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), and Center for Devices and Radiological Health (CDRH) each issues IND or IDE numbers using a similar format, we expressed in the NPRM our belief that, for purposes of registration with *ClinicalTrials.gov,* a complete, unambiguous IND or IDE number must include the name of the FDA center that issued it. In addition, if several clinical trials are conducted under a single IND, each such clinical trial may have a different serial number assigned to it. We noted that any such serial number must also be specified to avoid confusion. However, the NPRM explained that if multiple serial numbers are assigned to a single IND (*e.g.,* to reflect different clinical trials, protocols, or protocol amendments), the responsible party should submit only the first serial number that corresponds to the clinical trial being registered (79 FR 69626).

Commenters addressed the Food and Drug Administration IND or IDE Number data element. One commenter suggested that the final rule remove the proposed requirement to provide the name or abbreviation of the FDA center

with which the IND or IDE is filed. Another commenter requested clarification on whether submitting an IRB registration number in place of an IDE number or the FDA center information would be sufficient for clinical trials of nonsignificant risk devices subject to FDA abbreviated IDE requirements. We proposed requiring the FDA center name as a sub-element of the Food and Drug Administration IND or IDE Number data element because CDER, CBER, and CDRH all issue IND or IDE numbers using a similar format. We also recognize that not all applicable clinical trials will be conducted under an IND or IDE (*e.g.,* ''IND-exempt'' trials) and therefore would permit a responsible party to indicate that a particular trial is not being conducted under an FDA IND or IDE (*i.e.,* the responsible party would indicate ''no'' for this sub-element). We clarify that the FDA IND or IDE Number only refers to the number that is assigned by one of the FDA centers. Because FDA does not assign an IDE number for a clinical trial of a non-significant risk device subject to FDA-abbreviated IDE requirements nor does it issue an IDE for a clinical trial conducted outside of the United States, a responsible party for such trials should indicate ''no'' for the U.S. Food and Drug Administration IND or IDE Number data element. One commenter suggested that the final rule require information on whether a trial is being conducted under an IND or BLA for all trials conducted in the United States. As proposed under the NPRM, all responsible parties would be required to indicate whether an applicable clinical trial is being conducted under an IND or IDE, regardless of whether trial facility locations are within or outside the United States or both. We do not require the submission of information about BLAs for this data element because they are submitted to FDA only after trial completion, when a manufacturer is seeking to obtain a license for marketing a biological product, and so would not be available during trial registration. We note, however, that section 402(j)(5)(B) of the PHS Act requires submissions of BLAs to FDA to be accompanied by a certification (*i.e.,* Form FDA 3674) that all applicable requirements of this part have been met and to include a list of appropriate NCT numbers for applicable clinical trials used to support the BLA. Another commenter suggested that the final rule require the inclusion of an IND number or IND-exempt status of a trial to accommodate the determination of which trials quality for coverage of routine care costs of clinical trials under the Affordable Care Act in 42 U.S.C. 300gg–8. As noted in the NPRM, we do not intend to make the Food and Drug Administration IND or IDE Number available in the posted record. However, we note that this information would be readily accessible in the PRS to a responsible party for its own records and could be used by the responsible party to support this need. After consideration of these comments, we retain the proposed definition in final rule, but we clarify that it means ''an indication of whether'' there is an IND or IDE for the clinical trial. We also change the name of the data element to ''U.S. Food and Drug Administration IND or IDE Number'' for clarity, sinces other countries also have governmental agencies named ''Food and Drug Administration'' (*e.g.,* Korea).

(D) *Human Subjects Protection Review Board Status.* Section § 11.10(b)(36) of the NPRM defined this data element as ''information to indicate whether a clinical trial has been approved by a human subjects protection review board or is exempt from human subjects protection review board approval. Human Subjects Protection Review Board Status must be listed as 'approved' if at least one human subjects protection review board has approved the clinical trial.'' While submission of this information is not required by section 402(j) of the PHS Act, we proposed to add this requirement pursuant to the authority given by section 402(j)(2)(A)(iii) of the PHS Act to modify the requirements for clinical trial registration information if such modification ''improves and does not reduce such clinical trial information.'' We expressed in the NPRM our belief that submission of the Human Subjects Protection Review Board Status to *ClinicalTrials.gov* would improve, and not reduce, clinical trial information by indicating to users of the data bank whether a clinical trial registered on *ClinicalTrials.gov* is undergoing or has undergone review by a human subjects protection review board. Inclusion of this information would inform potential human subjects of whether the clinical trials they find on *ClinicalTrials.gov* have undergone at least one human subjects protection review board review, have received the necessary approvals for human subjects research from at least one human subjects protection review board, or were exempt from such review. We stated in the NPRM that the responsible party would be required to select from the following limited set of options intended to cover all possible statuses: ''Request not yet submitted'' (review board approval is required but has not yet been requested); ''Submitted, pending'' (review board approval has been requested but not yet granted); ''Submitted, approved'' (review board approval has been requested and obtained); ''Exempt'' (an exemption in accord with applicable law and regulation has been granted); ''Submitted, denied'' (review board has denied the approval request); and ''Submission not required'' (review board approval is not required because the study is not subject to laws, regulations, or applicable institutional policies requiring human subjects review). No ''other'' option was proposed. We requested comments on whether this menu of options adequately captured all possible review statuses for clinical trials that would be subject to this regulation (79 FR 69627).

The NPRM stated that the status would be listed as ''approved'' if at least one human subjects protection review board has approved the clinical trial. To clarify for users that the human subjects protection review board status pertains to only one human subjects protection review board, we would indicate that fact on *ClinicalTrials.gov* and instruct potential human subjects to communicate with the site-specific point-of-contact or the central contact for the clinical trial (included as part of the Facility Information data element that is submitted as part of clinical trial information under § 11.28(a)(2)(iii)(C)) in order to determine the status of human subjects protection review board review at other sites of interest. We indicated that we believe this approach will provide users with important information about human subjects review without burdening responsible parties with updating information on multiple sites (79 FR 69627). Some commenters proposed that the final rule require the submission of more detailed information for the Human Subjects Protection Review Board Status data element and display that information on the posted record, with one suggesting that public access to such information would be helpful for patients as well as for promoting the use of central IRBs for multicenter trials. As discussed, we believe that the proposed approach strikes the appropriate balance by providing users with the important information that at least one human subjects protection review board has reviewed and approved a trial without burdening responsible parties with the need to submit and update more detailed information for each board (up to one per facility). Therefore, we retain the proposed approach in the final rule.

We note that an applicable clinical trial could be registered prior to human subjects protection review board approval by indicating that the status is Request not yet submitted; Submitted, pending; or Exempt. If the status subsequently changes, the responsible party would be required, consistent with § 11.64(a)(1), to update the Human Subjects Protection Review Board Status data element not later than 30 calendar days after the change. If any IRB is still providing oversight for at least one site, the status of the trial would not be suspended even if such action is taken in relation to another site. We will continue to make available, as optional data elements, more detailed information about IRB approval, such as the name of the IRB, to support a responsible party's and/or an organization's tracking needs.

(E) *Record Verification Date.* Section § 11.10(b)(37) of the NPRM defined Record Verification Date as ''the date upon which the responsible party last verified the clinical trial information in the entire *ClinicalTrials.gov* record for the clinical trial, even if no additional or updated information was submitted at that time.'' This data element is required by section 402(j)(2)(A)(ii)(IV)(cc) of the PHS Act to be submitted as part of clinical trial information at the time of registration, but it does not define the term. In the NPRM, we expressed our belief that the record verification date is intended to be submitted as a separate data element that indicates to users of the data bank how recently the information for a particular clinical trial was verified and, hence, whether it may be out of date. We stated our intent to collect and post publicly the Record Verification Date data element on *ClinicalTrials.gov* (79 FR 69628).

We proposed requiring responsible parties to include the Record Verification Date data element as part of the initial submission of clinical trial registration information to *ClinicalTrials.gov* and to update it any time the responsible party reviews the complete clinical trial record for accuracy, such as when making a periodic review of an entire clinical trial record. However, if the responsible party submits updates to one or more data elements without reviewing the accuracy of the rest of the record, the Record Verification Date data element would not be updated. We noted that the proposed approach would not require a responsible party to review records more frequently or regularly than would be needed in order to update submitted information as specified in § 11.64 (should the responsible party use this method to help ensure that updates are submitted on time), but it would require that the Record Verification Date be updated if the complete record was reviewed for accuracy during such an update (79 FR 69628).

One commenter requested that we delete the word ''entire'' from the definition so that the responsible party is not required to review all data in the record any time the responsible party reviews some of the information. We agree with the commenter's point that a responsible party is not required to review all data each time a record is accessed. We believe, however, that the proposed definition makes it clear that the record verification date needs to be updated only when the responsible party does review the entire record, not just part of the record. This data element allows users to determine when all of the data submitted in the record was last reviewed and verified by the responsible party. Therefore, we maintain the NPRM definition in the final rule, but we note that § 11.64 of the final rule specifies that ''Record Verification Date must be updated any time the responsible party reviews the complete set of submitted clinical trial information for accuracy and not less than every 12 months, even if no other updated information is submitted at that time.''

(F) *Responsible Party Contact Information.* In § 11.10(b)(38) of the NPRM, we described Responsible Party Contact Information as ''[a]dministrative information to identify and allow communication with the responsible party by telephone, email, and regular mail or delivery service. Responsible Party Contact Information includes the name, official title, organizational affiliation, physical address, mailing address, phone number, and email address of the individual who is the responsible party or of a designated employee of the organization that is the responsible party.'' Section 402(j)(1)(B) of the PHS Act requires the Secretary to develop a mechanism ''by which the responsible party for each applicable clinical trial shall submit the identity and contact information of such responsible party to the Secretary at the time of submission of clinical trial information. . . .'' Using the authority in section 402(j)(2)(A)(iii) of the PHS Act, we proposed to modify the requirements for clinical trial information submitted at the time of registration to require responsible parties to submit Responsible Party Contact Information. As noted in the NPRM, we believe that the addition of this information will improve and not reduce clinical trial information by providing a mechanism for the Agency to communicate with the responsible party about submitted information, which can improve its quality, accuracy, and completeness. We noted that we do not intend to post the physical address, mailing address, phone number or email address of the responsible party (79 FR 69628). We received no comments on this data element and therefore maintain it in the final rule. In general, we intend to post the name of the responsible party if the responsible party is an individual (*e.g.,* a sponsor-investigator who holds the IND or IDE for a clinical trial or a designated principal investigator). We would post the name of the responsible party, along with the Responsible Party, by Official Title data element as specified in § 11.28(a)(2)(iii)(B) of the final rule, which section 402(j)(2)(A)(ii)(III)(bb) of the PHS Act requires to be made publicly available. We believe that the posting of the individual's name is necessary to avoid ambiguity; for example, if the responsible party is a university professor, there may be a number of individuals with the same title and affiliation (professor of medicine at ABC University). Posting the name of the individual when an individual is the responsible party would also be consistent with posting the name of the entity when an entity is the responsible party of an applicable clinical trial. The Responsible Party Contact Information data element would be required to be updated as specified in § 11.64.

Data elements that were suggested in public comments but not incorporated into the final rule are discussed below.

Bioequivalence and Bioavailability. One commenter requested the addition of data elements to identify bioequivalence and bioavailability studies and to indicate specific biomarkers relevant to the population studied. We note that *ClinicalTrials.gov* currently offers an optional registration data element, Study Classification, that includes both ''Bio-equivalence'' and ''Bio-availability'' as options. Biomarkers that are the focus of a study may be listed in the Primary Disease or Condition Being Studied in the Trial, or the Focus of the Study data element specified in proposed § 11.48(a)(1)(ix) and defined in proposed § 11.10(b)(9). We also note that biomarkers may be described in the context of outcome measures that are evaluated in the clinical trial. Otherwise, responsible parties could provide such information voluntarily as part of an optional data element (*e.g.,* Detailed Description). Because responsible parties can submit

this information using optional data elements, and consistent with our goal to minimize the number of required data elements, we do not require the submission of this information in the final rule. We understand the growing interest in and research on biomarkers and will continue to evaluate this topic and ways to further optimize the collection, retrieval, and display of such information.

Individual Participant Data (IPD) Availability. One commenter requested that the final rule include an optional data element for indicating whether IPD or CSRs are being made available to others and, if so, the location of the data and contact information. In December 2015, *ClinicalTrials.gov* added the following optional data elements that allow responsible parties to provide information about their plans for sharing IPD and to describe where data sets and/or study documents are available: Plan to Share Data? and Available Study Data/Documents. Because responsible parties can choose to submit this information using the optional data elements, and consistent with our goal to minimize the number of required data elements, we do not include these data elements in the final rule.

Other Trial Characteristics. Several commenters suggested that whether a registered trial is ''for profit'' should be clearly labeled on the posted record on *ClinicalTrials.gov*. We are not aware of any standard approaches for defining a trial's profit status (*e.g.,* ''for profit'' or ''non-profit'') and the commenters did not suggest any operational definitions. In addition, there are many features of a trial's sponsor that may be of interest to potential participants, as well as those interested in the study's results; *ClinicalTrials.gov* can help identify the trial and its sponsor but cannot provide all potentially relevant information. One other commenter recommended adding a data element that could be used for searching for trials of genetic therapies. We note that the Intervention Type data element defined in § 11.10(b)(13) includes a ''genetic'' (including gene transfer, stem cell and recombinant DNA) option that a responsible party could choose to identify a genetic therapy intervention. For these reasons, we are not adding additional data elements to include other trial characteristics, but we will consider providing an Advanced Search feature in the future that would allow users to search *ClinicalTrials.gov* for registered studies by Intervention Type.

Schedule of Events. One commenter suggested that the Agency consider adding a ''schedule of events'' data element that would provide information for participants about the medical care that will be covered in a study. While we understand that this information could be important for a potential participant, we believe it is more appropriate for this information be provided by the study contact at the time that potential participants and/or their health care providers are seeking further information about the study. Accordingly, we are not including this data element in the final rule.

§ 11.28(b)—Pediatric Postmarket Surveillance of a Device Product That Is Not a Clinical Trial

Overview of Proposal

(b) *Data elements required to register a pediatric postmarket surveillance of a device product that is not a clinical trial.* Proposed § 11.28(b) specified the clinical trial information that must be submitted to *ClinicalTrials.gov* to register a pediatric postmarket surveillance of a device that is not a clinical trial, as defined in this part, but is required to be registered under proposed § 11.22. Section 801(c) of FDAAA recognizes that not all of the clinical trial information specified in section 402(j) of the PHS Act or proposed in this rule will apply to all pediatric postmarket surveillances of a device and directs the Secretary to issue guidance explaining how the registration and results information submission provisions of section 402(j) of the PHS Act apply to a pediatric postmarket surveillance of a device that is not a clinical trial. As stated in the NPRM, the Agency intended for the discussion of the proposed sections related to pediatric postmarket surveillances of a device to provide draft guidance. In 21 CFR 822.3, ''postmarket surveillance'' is defined as the ''active, systematic, scientifically valid collection, analysis, and interpretation of data or other information about a marketed device.'' The Agency interpreted a pediatric postmarket surveillance of a device as a postmarket surveillance of a device used in a pediatric population (*i.e.,* patients who are 21 years of age or younger at the time of diagnosis or treatment) (see 21 U.S.C. 360j(m)(6)(c)). The clinical trial information specified in proposed § 11.28(a) and defined in proposed § 11.10(b) would apply to any pediatric postmarket surveillance of a device that is a clinical trial (*i.e.,* Study Type would be ''interventional''). However, because not all pediatric postmarket surveillances under section 522 of the FD&C Act are clinical trials, as defined in this part, many of the data elements listed in proposed § 11.28(a) or the definitions proposed in § 11.10(b) may not apply. Therefore, proposed § 11.28(b) specified a more limited set of data elements required to register a pediatric postmarket surveillance of a device that is not a clinical trial; moreover, it also modified the definitions of certain data elements that were defined in proposed § 11.10(b) (79 FR 69629).

In general, the proposed definitions of these data elements were consistent with the definitions of the named data elements in proposed § 11.10(b); however, we had modified them, where appropriate, to better match the characteristics of pediatric postmarket surveillances of a device that are not clinical trials. For example, Study Start Date, which was defined in proposed § 11.10(b)(16) for a clinical trial as ''the estimated date on which a clinical trial will be open to enrollment of human subjects, or the actual date on which the first human subject was enrolled,'' was defined in proposed § 11.28(b)(1)(xi) as the ''date on which FDA approves the postmarket surveillance plan, as specified in 21 CFR 822.19(a) (or any successor regulation).'' Similarly, the definition of Completion Date in section 402(j)(1)(A) of the PHS Act and proposed § 11.10(b)(17) generally would not apply to a pediatric postmarket surveillance of a device that is not a clinical trial; therefore, in proposed § 11.28(b)(1)(xii) we proposed to require submission of the Completion Date data element, which was defined as ''[t]he estimated date on which the final report summarizing the results of the pediatric postmarket surveillance of a device is expected to be submitted to FDA. Once the final report has been submitted, the actual date on which the final report is submitted to FDA.'' The Agency considered the proposed list of required data elements for a pediatric postmarket surveillance of a device that is not a clinical trial to be the most inclusive set of data elements that could be expected to apply to all pediatric postmarket surveillances of a device that are not clinical trials, regardless of the design of the surveillance. The proposed required information would allow users to access records of pediatric postmarket surveillances of a device that are not clinical trials by conducting searches using a number of relevant criteria, retrieve basic descriptive information about the surveillances, and find a point-of-contact for additional information. We did not propose the submission of those data elements listed under section 402(j)(2)(A)(ii) of the PHS Act that are not expected to apply to all

pediatric postmarket surveillances of a device that are not clinical trials. For example, Study Phase is relevant only to clinical trials involving drugs. The specific elements of Study Design (*e.g.,* Interventional Study Model, Allocation, Masking, Single Arm Controlled?) would not apply to most studies that are not interventional clinical studies (*i.e.,* clinical trials). Eligibility Criteria, Age, and Gender may not be defined specifically for the study population in a pediatric postmarket surveillance of a device that is not a clinical trial. Enrollment would not be relevant to a pediatric postmarket surveillance of a device that takes the form of a literature review. We noted that we expect that some information about the study design and relevant study population would be included in the brief summary of the pediatric postmarket surveillance of a device. We invited comments on alternative approaches for specifying the registration requirements for a pediatric postmarket surveillance of a device that is not a clinical trial (79 FR 69629).

Comments and Response

One commenter suggested that the registration data elements required to be submitted for a pediatric postmarket surveillance of a device that is not a clinical trial in proposed § 11.28(b) be replaced in the final rule with the same set of data elements required for clinical trials as specified in proposed § 11.28(a). The Agency disagrees with this suggestion. As described in the preamble, not all pediatric postmarket surveillances of a device product under section 522 of the FD&C Act are clinical trials. For such pediatric postmarket surveillances of a device product, many of the data elements for clinical trials listed in proposed § 11.28(a) and defined in proposed § 11.10(b) would not apply. Therefore, we specified in proposed § 11.28(b), and retain in the final rule, a limited set of registration data elements that would more likely apply across all pediatric postmarket surveillances of a device product, and we modified the definitions in proposed § 11.10(b) accordingly.

Final Rule

Taking into consideration the commenter's suggestions and the statutory requirements for what constitutes clinical trial registration information, § 11.28(b) of the final rule retains the data elements proposed in the NPRM but modifies some of the names and definitions to improve clarity and for consistency with the data elements named in § 11.28(a) and defined in § 11.10(b) of the final rule. Section 11.28(b) of the final rule identifies the structured information, or data elements, that constitute clinical trial information that a responsible party must submit in order to register a clinical trial. While the full set of data elements from the NPRM is maintained in the final rule, we have modified some of the names and definitions. For example, we have clarified that ''device'' means ''device product'' and the proposed name of Whether the Study is a Pediatric Postmarket Surveillance of a Device data element in § 11.28(b)(1)(v) of the NPRM has been renamed ''Pediatric Postmarket Surveillance of a Device Product'' throughout the final rule (*i.e.,* in §§ 11.10(b)(8), 11.28(a), 11.28(b), 11.60(b)(2)(i)(B)) for clarity and convenience, but the proposed definition is maintained in the final rule. Conversely, while the name of the Unique Protocol Identification Number data element has been retained, the definition has been modified from ''the unique identification number'' to ''the unique identifier'' for accuracy (*i.e.,* is not limited to numbers).

As set forth in § 11.28(b) of the final rule, to register a pediatric postmarket surveillance of a device product that is not a clinical trial, the responsible party must provide the following data elements: (1) Brief Title; (2) Official Title; (3) Brief Summary; (4) Study Type; (5) Pediatric Postmarket Surveillance of a Device Product; (6) Primary Disease or Condition Being Studied, or the Focus of the Study; (7) Intervention Name(s); (8) Other Intervention Name(s); (9) Intervention Description; (10) Intervention Type; (11) Study Start Date; (12) Primary Completion Date; (13) Name of the Sponsor; (14) Responsible Party, by Official Title; (15) Contact Information; (16) Unique Protocol Identification Number, if any; (17) Secondary ID; (18) Human Subjects Protection Review Board Status; (19) Record Verification Date; and (20) Responsible Party Contact Information. Consistent with the elaboration of these data elements in Section IV.B.4 of the preamble, for a pediatric postmarket surveillance of a device product that is not a clinical trial the Study Type must be designated as ''observational'' and Pediatric Postmarket Surveillance of a Device Product must indicate ''yes.''

In addition, for a pediatric postmarket surveillance of a device product that is not a clinical trial, we recommend that the responsible party submit any other registration information data elements that are consistent with the surveillance design and are capable of being accepted by *ClinicalTrials.gov.* For example, for a pediatric postmarket surveillance of a device product that takes the form of a prospective observational study, information such as the location(s) of the surveillance, its eligibility criteria, the recruitment status, and its outcome measures would also be relevant and should be submitted. We believe the public would be best served if additional descriptive information about these pediatric postmarket surveillances of a device product were included in the data bank, but, given the lack of experience to date, we cannot at this time specify what additional information would be relevant to a particular type of pediatric postmarket surveillance of a device product that is not a clinical trial.

§ 11.28(c)—Expanded Access Records

Overview of Proposal

(c) *Data elements required to create expanded access records.* Proposed § 11.28(c) described the clinical trial information that must be submitted to *ClinicalTrials.gov* to create an expanded access record when a responsible party registers an applicable drug clinical trial that studies an unapproved drug or unlicensed biological product that is available via an expanded access program under section 561 of the FD&C Act to those who do not qualify for enrollment in the clinical trial. However, because expanded access programs do not share all of the characteristics of clinical trials, as defined in this part, many of the data elements listed in proposed § 11.28(a) or their definitions in proposed § 11.10(b) do not apply. Therefore, proposed § 11.28(c) specified a limited set of data elements required to create an expanded access record; moreover, it also modified the definitions of certain data elements in proposed § 11.10(b). Overall, in the NPRM we considered the proposed set of data elements required to create an expanded access record to be the most inclusive that would be relevant to all expanded access programs (other than individual-patient access), regardless of design, and helpful to users of *ClinicalTrials.gov* who wish to determine whether they may be eligible to receive an investigational drug through an expanded access program and to obtain additional information about such access. The descriptions of the data elements in the NPRM generally paralleled the definitions of the data elements in proposed § 11.10(b) that are required to be submitted when registering a clinical trial under proposed § 11.28(a), but were modified in proposed § 11.28(c) to refer to expanded access programs rather than

clinical trials and to be limited to expanded access programs for drugs and biologics. One data element that was not defined in proposed § 11.10(b) but is required to be submitted for expanded access records only is the Expanded Access Status data element. We invited comments on whether the proposed list of options for this data element was sufficient to describe the status of an expanded access program (79 FR 69630).

We proposed requiring the submission of information to create an expanded access record using the statutory authority in section 402(j)(2)(A)(iii) of the PHS Act, which allows the Secretary by regulation to modify the requirements for clinical trial registration information if the Secretary provides a rationale why such a modification ''improves and does not reduce such clinical trial information.'' Information about the availability of expanded access is a data element that a responsible party is required to submit under section 402(j)(2)(A)(ii)(II) of the PHS Act and thus meets the definition of ''clinical trial information'' as that term is used in section 402(j)(1)(A)(iv) of the PHS Act. We noted in the NPRM that we think these additional data elements describing expanded access would improve and not reduce clinical trial information by providing users with more complete and consistent information about expanded access programs for drugs studied in applicable clinical trials than would be available pursuant to section 402(j)(A)(ii)(II)(gg) of the PHS Act alone. We further concluded that the clinical trial information required under proposed § 11.28(c), to be submitted by creating a separate expanded access record in *ClinicalTrials.gov,* under section 402(j)(2)(B)(iv) of the PHS Act would help ensure that the public can more easily use the data bank to determine whether there is expanded access to a drug and to compare different expanded access programs. In addition, this approach was consistent with the practice followed prior to the enactment of FDAAA, when those registering trials in compliance with FDAMA submitted expanded access information in the form of expanded access records on *ClinicalTrials.gov.* We proposed that in the rare instance in which an expanded access program for a drug met all of the elements of an applicable drug clinical trial, the expanded access program would have to be registered as an applicable drug clinical trial (79 FR 69630). In developing the NPRM, we considered alternative approaches, such as requiring the responsible party to submit the name, phone number, and email address of a point-of-contact or Web site for information about the expanded access program for each clinical trial of a drug that has such a program. However, we concluded that this approach would not ensure that complete information is available and, by including such information as part of clinical trial registration information, we can better ensure that the information is kept up-to-date as required in proposed § 11.64. Another alternative we considered was to require responsible parties to enter the additional data elements describing expanded access with every applicable clinical trial of a drug or biological product for which expanded access is available. Under our proposal, however, in situations in which multiple applicable clinical trials study the same drug that is available via the expanded access program, the expanded access record would be submitted only once. Thereafter, any responsible party could link the expanded access record to the clinical trial record(s) using the NCT number assigned to the expanded access record, thereby reducing the burden a responsible party faces when providing information about expanded access for multiple records (79 FR 69631).

As explained in Section IV.B.4 of the NPRM, in the discussion of the Availability of Expanded Access data element, the expanded access record generated on *ClinicalTrials.gov* pursuant to the submission of the data elements at proposed § 11.28(c) would be assigned its own NCT number and would be searchable and retrievable independent of the record(s) for the clinical trial(s) that study(ies) the drug or biological product for which expanded access is offered. To allow *ClinicalTrials.gov* to establish a link between the expanded access record and the clinical trial record(s), the responsible party(ies) for any applicable clinical trials of the drug available via expanded access would be required to include the NCT number that is assigned to the expanded access record as part of the registration information submitted for that clinical trial. In this way, the expanded access record could be linked in this fashion to multiple applicable clinical trials that study the drug or biological product that is available via the expanded access program. We sought comments on this proposed approach.

We also proposed that expanded access information for a medical device that was studied in an applicable device clinical trial could be submitted voluntarily under section 402(j)(4)(A) of the PHS Act to create an expanded access record for the device. (79 FR 69630) We further proposed that if a responsible party chose to submit this information, the responsible party would be required to submit all of the data elements that are required for expanded access to a drug in § 11.28(c), and that such expanded access records for investigational devices would be required to be updated in accordance with § 11.64(b)(1)(v).

Comments and Response

We received comments addressing the proposed content of an expanded access record. A commenter suggested that NIH and FDA should streamline and standardize expanded access information for patients and that NIH should collect and post the results obtained through expanded access programs on *ClinicalTrials.gov.* A commenter proposed linking expanded access records to the FDA application forms for expanded access programs. Section 11.28(c) of the NPRM represented our efforts to develop a streamlined and standardized approach to presenting information on *ClinicalTrials.gov* about expanded access programs. The proposed set of data elements represents, for the most part, a subset of the registration data elements required for an applicable clinical trial of a drug under proposed § 11.28(a). These proposed data elements were selected to represent key information that would generally apply across all expanded access programs. We stated in the NPRM that these data elements would allow *ClinicalTrials.gov* to display a structured summary about each expanded access program in a consistent format that would allow users to review important information quickly and easily (*e.g.,* eligibility criteria, disease or condition, intervention name and description). Regarding the suggestion to require the submission of results from expanded access use, as discussed in Section IV.A.5, we have concluded that use of an investigational drug product (including a biological product) under expanded access will not be considered an applicable clinical trial. Therefore, no expanded access use of an investigational drug product (including a biological product) will be subject to the results information submission requirements of this rule. We will consider providing links to additional resources about expanded access such as FDA application forms on the *ClinicalTrials.gov* public Web site, as suggested.

Final Rule

Taking into consideration the commenters' suggestions and the statutory requirements for what constitutes clinical trial registration information, § 11.28(c) of the final rule modifies the set of data elements from the NPRM that a responsible party must submit in order to create an expanded access record as required in § 11.28(a)(2)(ii)(H) of the final rule. Some of the data elements in § 11.28(c) that have been modified from what was proposed address the modification described in section IV.B.4 of this preamble in the discussion of the Availability of Expanded Access data element, which requires submission of an expanded access record for all expanded access types, including when expanded access is available for individual patients, including emergency use. Other modifications include some of the names and definitions of the proposed data elements to improve clarity and consistency with the data elements named in § 11.28(a) and defined in § 11.10(b) of the final rule, including the clarification that ''drug'' means ''drug product'' and that ''device'' means ''device product''. In addition, we provide further elaboration on the purpose of some data elements and how a responsible party can meet the data element requirements. Section 11.28(c) of the final rule also clarifies that expanded access records are only required to be created and updated by a responsible party who is both the manufacturer of the investigational drug product (including biological product) that is available through expanded access and the sponsor of an applicable clinical trial of that investigational drug product (including biological product), as specified in §§ 11.10(b)(28) and 11.28(a)(2)(ii)(H) of the final rule. Finally, we exclude from the final rule the proposed provision regarding the voluntary submission of expanded access information for a medical device under section 402(j)(4)(A) of the PHS Act, and we provide a further explanation below.

The Expanded Access Type data element, which was not proposed in the NPRM, is defined in § 11.28(c)(1)(x) of the final rule as ''[t]he type(s) of expanded access for which the investigational drug product (including a biological product) is available as specified in § 11.10(b)(28).'' For this data element, responsible parties would be required to select one or more options from the following limited set: ''individual patient'' (*i.e.,* expanded access for individual patients, including for emergency use, as specified in 21 CFR 312.310), ''intermediate'' (*i.e.,* expanded access for intermediate-size patient populations, as specified in 21 CFR 312.315), or ''treatment use'' (*i.e.,* expanded access for widespread treatment use under a treatment IND or treatment protocol, as specified in 21 CFR 312.320). As described in section IV.B.4 of this preamble, in the discussion of the Availability of Expanded Access data element, the final rule expands the proposed requirement to provide expanded access records for all types of expanded access available for an unapproved drug product (including a biological product). In light of this expansion, the Expanded Access Type data element is required to indicate the particular type(s) of expanded access under which an investigational drug product (including a biological product) is available. Additionally, the submission of certain expanded access record data elements specified in § 11.28(c)(2) are not required if the Expanded Access Type indicates that expanded access is available only for individual patients, including for emergency use. Thus, the Expanded Access Type data element facilitates identifying which information must be provided, specific to the type of availability of expanded access. For these reasons, this new registration data element is authorized by section 402(j)(2)(A)(ii) of the PHS Act because requiring it improves and does not reduce the clinical trial information.

While the other required data elements from the NPRM are maintained in the final rule, we have modified some of the names and definitions to be consistent with other modifications throughout this final rule. For example, the proposed Gender data element in § 11.28(c)(2)(ii) of the NPRM is renamed ''Sex/Gender'' here and throughout the final rule to be consistent with the same modification described in section IV.B.4 of this preamble and § 11.28(a)(2)(ii) of the final rule. Conversely, while the name of the Unique Protocol Identification Number data element is maintained, the definition has been modified from ''the unique identification number'' to ''the unique identifier'' for accuracy (*i.e.,* is not limited to numbers) and the explanation modified to explain it can also be an identifier of the expanded access record. Specifically, if the sponsor did not assign a unique identifier to the availability of its investigational drug product (including a biological product) for expanded access use, an identifier for the expanded access record must be provided. This identifier is composed of numbers and/or letters and is needed to uniquely identify an expanded access record in the PRS prior to submission and assignment of an NCT number. The Agency will provide additional instructions at *https://prsinfo.clinicaltrials.gov* (or successor site) to assist sponsors in creating a unique identifier for the expanded access record if the sponsor did not assign an identifier to the expanded access. Similarly, instructions will also be available at *https://prsinfo.clinicaltrials.gov* (or successor site) for sponsors needing to create a Brief Title as specified in § 11.28(c)(1)(i), which is used for identification of the expanded access record in the PRS and on the publicly posted study record.

As set forth in § 11.28(c) of the final rule, if expanded access is available for an intermediate-size patient population as specified in 21 CFR 312.315) or through a treatment IND or treatment protocol (as specified in 21 CFR 312.320), a responsible party who is both the manufacturer of an investigational drug product (including a biological product) that is available through expanded access and the sponsor of an applicable clinical trial of that investigational product must provide the following data elements to create an expanded access record: (1) Brief Title; (2) Official Title; (3) Brief Summary; (4) Study Type (which is ''expanded access'' for this type of record); (5) Primary Disease or Condition; (6) Intervention Name(s); (7) Other Intervention Name(s); (8) Intervention Description; (9) Intervention Type (which is typically ''drug''), (10) Expanded Access Type; (11) Eligibility Criteria; (12) Sex/Gender; (13) Age Limits; (14) Expanded Access Status; (15) Name of the Sponsor; (16) Responsible Party, by Official Title; (17) Contact Information; (18) Unique Protocol Identification Number; (19) Secondary ID; (20) U.S. Food and Drug Administration IND Number; (21) Record Verification Date; and (22) Responsible Party Contact Information.

If expanded access is only available for individual patients, including for emergency use as specified in 21 CFR 312.310, then only the following data elements are required: (1) Brief Title; (2) Brief Summary; (3) Study Type; (4) Intervention Name; (5) Intervention Type; (6) Expanded Access Type; (7) Expanded Access Status; (8) Name of Sponsor; (9) Responsible Party, by Official Title; (10) Contact Information; (11) Unique Protocol Identification Number; (12) U.S. Food and Drug Administration IND number, if

applicable; (13) Record Verification Date; and (14) Responsible Party Contact Information. This more limited set of expanded access information is sufficiently detailed to address the availability of an investigational drug product (including biological product) under individual patient expanded access.

If information necessary to complete certain data elements required for submitting an expanded access record under § 11.28(c)(1)–(4) are unknown to the responsible party because the expanded access availability is managed by a different entity, the responsible party will need to consult with NIH concerning those data elements before submitting the expanded access record, Instructions for contacting NIH will be available at *https://prsinfo.clinicaltrials.gov* (or successor site). We also note that the definition of Official Title specified in § 11.28(c)(1)(ii) has been clarified to indicate it only needs to be provided if one exists (*i.e.,* if there is an official title then it must be provided; if there is not an official title, the data element does not need to be provided). Similarly, the U.S. Food and Drug Administration IND Number data element has been modified to allow a responsible party to specify whether the expanded access is being conducted under an IND, but to allow for certain elements related to the IND to be provided ''if applicable''.

Expanded Access Status is another data element that is required to be submitted only for expanded access records and is not defined in § 11.10(b). It is defined in § 11.28(c)(2)(iv) of the final rule to mean ''[t]he status of availability of the investigational drug product (including a biological product) through expanded access.'' When submitting this data element, responsible parties are required to select from the following limited set of options for describing the current status of availability of the investigational drug product through the expanded access program: ''Available'' (expanded access is currently available), ''No longer available'' (expanded access was available previously but is not currently available and is not expected to be available in the future), ''Temporarily not available'' (expanded access was previously available, is not currently available, but is expected to be available in the future), and ''Approved for marketing'' (expanded access was available previously but is not currently available because the drug or device has been approved, licensed, or cleared by FDA).

We have further considered the proposal regarding the voluntary submission of expanded access information under section 402(j)(4)(A) of the PHS Act for unapproved or uncleared device products that are studied in an applicable device clinical trial and have decided not to include this provision in the final rule under § 11.60. The Availability of Expanded Access data element defined in § 11.10(b)(28) and specified in § 11.28(a)(2)(ii)(H) of the final rule is a data element that is specific to the availability of expanded access for an applicable drug clinical trial of an investigational drug product (including a biological product). Similarly, the obligations in § 11.28(c) to create an expanded access record are, consistent with section 402(j)(2)(A)(ii)(II)(gg) of the PHS Act, are specific to the provision of information when expanded access to an investigational drug product (including a biological product) is available under section 561 of the FD&C Act and 21 CFR 312.310 (for individual patients, including for emergency use), 21 CFR 312.315 (for an intermediate-size patient population), or 21 CFR 312.320 (under a treatment IND or treatment protocol). Therefore, for the purposes of the voluntary submission of expanded access information under section 402(j)(4)(A) of the PHS Act and § 11.60 for unapproved or uncleared device products that are studied in an applicable device clinical trial, ''complete clinical trial information'' does not include information about the availability of expanded access for the investigational device product.

We note that a responsible party for an applicable device clinical trial could choose to create an expanded access record for the investigational device product being studied in that trial if the investigational product is being made available under section 561 of the FD&C Act and 21 CFR 812.36. We intend to provide additional information at *https://prsinfo.clinicaltrials.gov* (or successor site) to clarify which data elements would apply in such a situation.

5. 11.35—By when will the NIH Director post clinical trial registration information submitted under § 11.28?

Overview of Proposal

According to section 402(j)(2)(D)(i) of the PHS Act, for applicable clinical trials, NIH is to post registration information not later than 30 days after the information is submitted. In the NPRM, we proposed in § 11.35(a) that NIH will post publicly the clinical trial registration information, except for certain administrative data, ''not later than 30 calendar days after the responsible party has submitted such information in accordance with § 11.24 of this part'' (79 FR 69631).

For an applicable device clinical trial of a device that was previously cleared or approved by FDA, section 402(j)(2)(D)(ii)(II) of the PHS Act requires registration information to be posted ''not later than 30 days after'' results information is required to be posted. The Agency interpreted section 402(j)(2)(D)(ii)(II) of the PHS Act as providing a deadline by which such registration information must be posted. The Agency considered the requirement to post registration information ''not later than 30 days after [results information] is required to be posted'' to be the last possible date on which it may post registration information and that it is permissible to post registration information prior to the deadline. The NPRM at § 11.35(b)(1) proposed that for an applicable device clinical trial of a device that was previously approved or cleared, NIH will publicly post the clinical trial registration information, except for certain administrative data, not later than 30 calendar days after clinical trial results information is required to be posted in accordance with proposed § 11.52 (79 FR 69631).

Section 402(j)(2)(D)(ii)(I) of the PHS Act stipulates that for an applicable device clinical trial of a device that has not previously been cleared or approved, registration information must be posted publicly not earlier than the date of clearance or approval of the device and not later than 30 days after such date. Proposed § 11.35(b)(2) reflected this statutory provision by stating that for an applicable device clinical trial of a device that has not been previously approved or cleared, ''NIH will post publicly at *ClinicalTrials.gov* the clinical trial registration information, except for certain administrative data, not earlier than the date of FDA approval or clearance of the device, and not later than 30 calendar days after the date of such approval or clearance.'' In the NPRM, we acknowledged that while postponing the posting of clinical trial registration information for applicable device clinical trials for a device that previously has not been approved or cleared may protect the commercial interests of device manufacturers, there are a number of situations in which those who conduct such clinical trials may prefer to make such information publicly available in the data bank prior to the time frames specified by section 402(j) of the PHS Act. Therefore, we invited comments from the public on how, given the statutory language of Section 402(j)(2)(D)(ii)(I) of the PHS Act,

the Agency may address the concerns of sponsors and responsible parties who wish to have clinical trial registration information for applicable device clinical trials of devices that previously have not been approved or cleared made publicly accessible in *ClinicalTrials.gov* when the responsible party so chooses (79 FR 69576).

In order to help NIH meet the posting deadline and identify the set of applicable device clinical trials for which registration information must be posted after approval or clearance of a device, the NPRM included a requirement in proposed § 11.64(b)(2) for the responsible party to update the U.S. FDA Approval, Licensure, or Clearance Status data element not later than 15 calendar days after a change in status has occurred. The responsible party would be required to update that data element for all applicable device clinical trials that study a device that was approved or cleared (79 FR 69631).

Comments and Response

We received comments on the specific question of when NIH should post clinical trial registration information. Some commenters supported and some opposed the proposed approach to determining which devices would be able to take advantage of the delayed posting available to devices that have not been previously approved or cleared. This topic is addressed in more detail in Section IV.B.4 of this preamble.

Some commenters indicated they did not support the delayed posting of registration information for devices that have not been previously cleared or approved. Delayed posting is outlined in Section 402(j)(2)(D)(ii)(I) of the PHS Act, which says that the Agency may not post publicly clinical trial registration information before the date of clearance or approval for an applicable device clinical trial of a device that was not previously cleared or approved. Section 11.35(b)(2) of the NPRM, and the final rule at § 11.35(b)(2)(i), reflect this limit. Other commenters argued that the delayed posting of clinical trial registration information provision in the statute should not be understood as a bar to consensual disclosure of such information if a device sponsor wishes to waive the right to delayed posting. The commenters noted that under circumstances where a party wishes to waive a statutory right, and that waiver would not frustrate the public purpose of that statute, courts have acknowledged that statutory rights intended to protect individual rights may be waived by the persons for whom the statute provides protection.

We agree with views expressed by commenters that because the delayed posting of registration information benefits the responsible party, the responsible party should be able to choose to authorize the Agency to make registration information available earlier. There may be any number of reasons a responsible party would wish to opt out of the delayed posting of registration information, such as to enhance patient enrollment or to meet the requirements for consideration by a journal abiding by ICMJE policy [Ref. 2]. Although Section 402(j)(2)(D)(ii)(I) of the PHS Act provides that the Director of NIH ''shall'' ensure that clinical trial information for an applicable device clinical trial of an unapproved or uncleared device is not posted on *ClinicalTrials.gov* earlier than the date of clearance or approval of the device, section 402(j)(2)(A)(iii) of the PHS Act gives the Secretary authority to modify by regulation the requirements for clinical trial information under paragraph (2), which includes the delayed posting provision in 402(j)(2)(D)(ii), so long as a rationale is provided for why the modification improves and does not reduce such clinical trial information. The Agency believes that allowing the responsible party to authorize that clinical trial registration information that would otherwise fall under the delayed posting provision be publicly posted prior to approval or clearance of the product would improve and not reduce such clinical trial information by making it accessible to the public earlier. This approach would strike the proper balance between affording the statutory protections of delayed disclosure to those responsible parties that would like to take advantage of it while promoting transparency of clinical trial registration information by allowing responsible parties to authorize earlier posting.

Pursuant to section 402(j)(2)(A)(iii) of the PHS Act, we are adding a new provision at § 11.35(b)(2)(ii) to incorporate this option for a responsible party to authorize early posting as well as a specific data element in § 11.28(a)(2)(i)(Q) that will be the mechanism through which a responsible party can indicate to the Director that it is authorizing the Director to publicly post its clinical trial registration information prior to U.S. FDA approval or clearance of the device product. See further discussion in this Section describing the final rule as well as in Section IV.B.4 of this preamble.

Final Rule

We have taken into consideration the commenters' suggestions and the statutory requirements for posting registration information in developing § 11.35 of the final rule. Section 11.35(a) states that the Director will post publicly at *ClinicalTrials.gov* the clinical trial registration information for an applicable drug clinical trial not later than 30 calendar days after the responsible party has submitted such information, as specified in § 11.24.

Section 11.35(b)(1), which covers posting of registration information for an applicable device trial of a device product that has been previously approved or cleared, has been modified from the NPRM for clarity. We have added the phrase ''as soon as practicable'' to indicate that NIH will post registration information for an applicable device clinical trial of a device product that previously was approved or cleared ''as soon as practicable, but not later than'' the statutory deadline outlined in section 402 (j)(2)(D)(ii)(II) or successor statute. Section 402(j)(2)(D)(ii)(II) stipulates that clinical trial registration information for an applicable device clinical trial of a device that was previously cleared or approved will be posted ''not later than 30 days after the clinical trial information under paragraph (3)(C) is required to be posted by the Secretary.'' The information referred to by ''in paragraph (3)(C)'' is basic results information. The additional phrase of ''as soon as practicable'' clarifies in the regulatory language the NIH's intent, described in the NPRM, to post registration information for such applicable device clinical trials as soon as practicable after submission, but not later than 30 calendar days after clinical trial results information is required to be posted. Posting this information prior to the deadline is consistent with the objectives of expanding the registry and results data bank by rulemaking, facilitating enrollment in clinical trials, and providing a mechanism to track subsequent progress of clinical trials. Conversely, waiting to post registration information for applicable device clinical trials of device products that were previously approved or cleared until after results information is required to be posted would delay access to information about such clinical trials and would eliminate the possibility for the data bank to be used to facilitate enrollment in such trials and to allow the public to track such trials while they are ongoing. We have also clarified that ''device'' means ''device product.''

Section 11.35(b)(2) covers posting of registration information for an applicable device trial of a device product that has not been previously

approved or cleared. Proposed § 11.35(b)(2) has been separated in the final rule into § 11.35(b)(2)(i) and § 11.35(b)(2)(ii). In these sections, we have clarified that ''device'' means ''device product.'' Additionally, § 11.35(b)(2)(i) adds a reference to the exception in § 11.35(b)(2)(ii) for earlier posting of registration information by the Director if authorized by the responsible party.

New § 11.35(b)(2)(ii) allows a responsible party for an applicable clinical trial that is initiated on or after the effective date of the rule to indicate to the Director, prior to the date of approval or clearance of the device product, that it is authorizing the Director to publicly post its clinical trial registration information that would otherwise be subject to delayed posting as specified in paragraph (b)(2)(i) prior to the date of FDA approval or clearance of the device product. Upon notification, in the form of the responsible party's submission of the Post Prior to U.S. FDA Approval or Clearance data element under § 11.28(a)(2)(i)(Q), the Director will post the clinical trial registration information, except for certain administrative data, as soon as practicable. Additionally, the Director intends to follow the timelines established by section 402(j)(2)(D)(i) of the PHS Act of posting the clinical trial registration information not later than 30 days after such submission. While this section of the statute refers to applicable drug clinical trials, it establishes a clear timeline between the submission of clinical trial registration information and its posting.

Two additional issues directly related to posting of registration information are briefly described further: (1) The administrative data elements that the Agency does not intend to post publicly and (2) the relationship of posting and quality control described in Section IV.D.3 of this preamble. First, section 402(j)(2)(A)(ii)(IV) of the PHS Act specifies that the Secretary ''may make publicly available as necessary'' administrative data that are submitted as part of clinical trial registration information. We interpret this provision to permit the Secretary to not post certain administrative data in the data bank if the data are not considered necessary for understanding the clinical trial or for recruitment. As noted for each data element discussed in Section IV.B.4 of this preamble, we do not believe it is necessary to make public the following administrative data and currently do not intend to post them publicly in *ClinicalTrials.gov* for any applicable clinical trials: (1) Food and Drug Administration IND or IDE Number and (2) Responsible Party Contact Information other than the name of the responsible party if the responsible party is an individual (as opposed to an entity). Second, as described in further detail in Section IV.D.3 of this preamble, we intend to continue a form of quality control review at the time of clinical trial information submission that is similar to the procedures we have been using for the past several years. We note here, however, that, because the quality control review process does not affect the statutory deadlines for submitting or publicly posting submitted clinical trial information, there will be cases in which submitted clinical trial information is posted even though the quality control review process has not concluded. Although we will post clinical trial registration information not later than 30 calendar days after submission, we will not assign an NCT number until the quality control review process has concluded. Thus, the clinical trial registration information will be posted to the *ClinicalTrials.gov* Web site without an NCT number. In addition, the clinical trial record will contain information that will be visible to those viewing the record on *ClinicalTrials.gov* to make it clear that the quality control review process has not concluded for the posted registration information.

Reflecting section 402(j)(2)(C) of the PHS Act, as codified in § 11.22, the timelines in § 11.35 apply only to clinical trials that are required to register with *ClinicalTrials.gov.* If a clinical trial is registered with *ClinicalTrials.gov* as a voluntary submission as specified in § 11.60, the registration information will be posted as soon as practicable after it has been submitted and reviewed as part of quality control review procedures.

C. Subpart C—Results Information Submission

Subpart C sets forth requirements and procedures related to the submission of results information. In addressing what constitutes results information, subpart C does not specify what results information must be collected while the applicable clinical trial or other clinical trial is being conducted, but rather spells out which elements of the collected data must be submitted and in what required format. Subpart C also specifies when NIH will post results information in *ClinicalTrials.gov* and what procedures may be used to request a waiver of any applicable requirements for results information submission. Below, we summarize each section of subpart C, summarizing its statutory basis, what we proposed in the NPRM, any public comments received on the proposal, and the approach we take in the final rule.

1. § 11.40—Who must submit clinical trial results information?

Overview of Proposal

Proposed § 11.40 required that the responsible party for an applicable clinical trial specified in proposed § 11.42 submit clinical trial results information for that clinical trial. This approach is consistent with section 402(j)(3)(E)(i) of the PHS Act (79 FR 69632).

Comments and Response

No comments were received on this section.

Final Rule

The final rule maintains § 11.40 as proposed.

2. § 11.42—For which applicable clinical trials must clinical trial results information be submitted?

Overview of Proposal

In the NPRM, § 11.42 detailed the applicable clinical trials for which results information would be required to be submitted in accordance with subpart C to *ClinicalTrials.gov,* unless the requirement is waived under proposed § 11.54 (79 FR 69632). Pursuant to section 402(j)(3)(D)(ii)(I) of the PHS Act, § 11.42 proposed to require the submission of results information for specified: (1) Applicable clinical trials of drugs that are approved under section 505 of the FD&C Act or licensed under section 351 of the PHS Act; and (2) applicable clinical trials of devices that are cleared under section 510(k) of the FD&C Act or approved under section 515 or 520(m) of the FD&C Act. Proposed § 11.42 also would have required the submission of results information for specified applicable clinical trials of drugs or devices that are not approved, licensed, or cleared for any indication (regardless of whether the sponsor seeks approval, licensure, or clearance). We noted that proposed § 11.42 pertains to section 402(j)(3)(D)(ii)(II) of the PHS Act, which directs that the Secretary establish through regulation whether or not results information must be submitted for applicable clinical trials of drugs and devices that have not been approved, licensed, or cleared by FDA, whether or not approval, licensure, or clearance is sought (79 FR 69632).

In the NPRM, § 11.42 proposed to require responsible parties to submit

results information for applicable clinical trials that are required to be registered with *ClinicalTrials.gov* under § 11.22 and that met one of the following criteria: (a) The completion date is on or after the rule's effective date (§ 11.42(a)); or (b) the completion date is prior to the effective date of this rule, the applicable deadline established by § 11.44 is on or after the effective date of the rule, and clinical trial results information is submitted on or after the effective date of the rule, consistent with the applicable deadline established by § 11.44 (§ 11.42(b)) (79 FR 69632). The NPRM also stated in the discussion of the effective date/compliance date (Section III.D) that for results information due prior to the rule's effective date under section 402(j)(3)(C) of the PHS Act, if the responsible party did not in fact submit these results by the effective date, then the responsible party would be required to submit the clinical trial results information specified by § 11.48 (79 FR 69593).

In addition, the NPRM proposed how the rule would handle an applicable clinical trial of a drug or device under study that was not approved, licensed, or cleared by FDA and reached its completion date prior to the effective date of the rule, but the product is subsequently approved, licensed, or cleared by FDA after the effective date. We proposed that responsible parties for such applicable clinical trials be required to submit clinical trial results information specified in § 11.48 by the earlier of 1 year after the completion date or 30 calendar days after the date of initial FDA approval, licensure, or clearance (79 FR 69594).

Comments and Response

We received a few comments on the issues specifically covered by proposed § 11.42. Those commenters suggested that results information submission should not be required for trials with results published in a peer-reviewed journal and that a hyperlink from *ClinicalTrials.gov* to the published study and lay summary of results would suffice. While results information submission to *ClinicalTrials.gov* is required by section 402(j) of the PHS Act independently of publication, *ClinicalTrials.gov* currently provides a number of optional data elements such as Citations and Links, which can be used to link a record to relevant trial results cited in publications or available at another Web site, respectively [Ref. 97]. We anticipate that these optional data elements will continue to be available on *ClinicalTrials.gov.*

We also received comments on issues relevant to proposed § 11.42. Several commenters suggested that the rule should require results information for applicable clinical trials completed at any time, in order to ensure public access to such results information for completed trials of drugs that are currently on the market. Applicable clinical trials initiated on or before September 27, 2007, or completed before December 26, 2007, are not required to register or submit results information under section 402(j) of the PHS Act. As discussed here and furthermore in Section III.B Submission of Results Information for Applicable Clinical Trials of Unapproved, Unlicensed, or Uncleared Products for Any Use and Section IV.F Effective Date, Compliance Date, and Applicability of Requirements in this Part in the preamble, in the final rule, the NIH requires results information submission from applicable clinical trials of products that were unapproved, unlicensed, or uncleared before the primary completion date but subsequently approved, licensed, or cleared after the primary completion date when the primary completion date is on or after the effective date of the final rule. That is, with this rule, we require results information from trials completed after the effective date, regardless of whether approval, licensure, or clearance of the studied product is sought. A related suggestion in comments was to require submission of results information from applicable clinical trials completed since the year 2000. The submission of results information pursuant to these regulations, from trials with a primary completion date before the effective date of the regulations, is not required. Submission of basic results information (as defined in 402(j)(3)(C) of the PHS Act) from applicable clinical trials has been a statutory requirement since September 27, 2008, however, and is required for applicable clinical trials with a primary completion date before the effective date of the final rule.

Finally, some commenters opposed the NPRM requirement that responsible parties who previously submitted results information for outcome measures would be required to comply with the final rule, anissue discussed in more depth in Section IV.F. of the preamble, Effective Date, Compliance Date, and Applicability of Requirements in this Part. As discussed in Section IV.F., the results information submission requirements that apply to an applicable clinical trial are determined by the date on which the trial reaches its actual primary completion date rather than when a responsible party submits results information.

Final Rule

Taking into consideration these submitted comments as well as the statutory requirements, we have modified § 11.42 in the final rule. We clarify which applicable clinical trials must submit results information according to the final rule and, consistent with the discussion in Section IV.F. of the preamble, we have made revisions and have restructured § 11.42 to address the differing requirements that apply to applicable clinical trials (and, if voluntarily submitted, other clinical trials). Section 11.42(a) applies to applicable clinical trials for which the studied product is approved, licensed, or cleared by FDA. If the primary completion date for such trial is before the effective date of the final rule, § 11.42(a)(1) requires clinical trial results information submission as specified in sections 402(j)(3)(C) and 402(j)(3)(I) of the PHS Act. If the primary completion date for such trial is on or after the effective date of the final rule, § 11.42(a)(2) requires clinical trial results information submission as specified in § 11.48. As discussed further in Section IV.F. on Effective Date, Compliance Date, and Applicability of Requirements in this Part, results information submission requirements are determined by the date on which the trial reaches its actual primary completion date. Thus, for trials that reach their primary completion date before the effective date of the final rule, results information submission is required as specified in sections 402(j)(3)(C) and 402(j)(3)(I) of the PHS Act, and for trials that reach their primary completion date on or after the effective date of the final rule, results information submission is required as specified in this final rule.

Section 11.42(b) applies to applicable clinical trials for which the studied product is not approved, licensed, or cleared by FDA. As discussed in Section III.B Submission of Results Information for Applicable Clinical Trials of Unapproved, Unlicensed, or Uncleared Products for Any Use and Section IV.E. Effective Date, Compliance Date, and Applicability of Requirements in this Part, such applicable clinical trials are not subject to results information submission requirements until the effective date of the final rule. Thus, § 11.42(b) only applies to applicable clinical trials for which the studied product is not approved, licensed, or cleared if those trials have a primary completion date on or after the effective date of the final rule. For such trials,

clinical trial results information is required to be submitted as specified in § 11.48.

We note that proposed § 11.42(b) had outlined scenarios in which the completion date of the trial is prior to the effective date of the rule and results information was required to be submitted according to the proposed rule. Under the simplified approach taken in the final rule, as discussed in Section IV.F., because determination of results information submission requirements relies on the primary completion date in relation to the effective date, proposed § 11.42(b) is no longer necessary. That is, there will be no scenarios in which the primary completion date is prior to the effective date of the rule and results information is required to be submitted according to the rule. We also note that the requirement to submit results information for applicable clinical trials with a primary completion date that is on or after the effective date, as specified in § 11.48, applies regardless of whether any results information, including for primary outcome measure(s), has been submitted before the effective date.

3. § 11.44—When must results information be submitted for applicable clinical trials subject to § 11.42?

Overview of Proposal

Proposed § 11.44 specified the deadlines for submitting results information for applicable clinical trials, implementing section 402(j)(3)(E) of the PHS Act. Proposed § 11.44(a) specified the standard submission deadlines for applicable clinical trials that are clinical trials subject to proposed § 11.42. Proposed § 11.44(b) and (c) described procedures for delaying the standard submission deadlines with certification when seeking approval, licensure, or clearance of a new use or initial approval, licensure, or clearance, respectively, of a drug (including a biological product) or device studied in an applicable clinical trial. Proposed § 11.44(d) specified the procedures for submitting partial results information, while § 11.44(e) described the process for requesting an extension of the results information submission deadline for good cause. Finally, proposed § 11.44(f) established the timeline for submitting results of a pediatric postmarket surveillance of a device that is not a clinical trial (79 FR 69632). Below we discuss each part of § 11.44 separately.

§ 11.44(a) Standard Submission Deadline

Overview of Proposal

Proposed § 11.44(a)(1) specified that, in general, the deadline for submitting results information for an applicable clinical trial would be 1 year after the completion date of the clinical trial. As explained in the NPRM, sections 402(j)(3)(E)(i)(I) and (II) of the PHS Act specify that results information is to be submitted not later than 1 year after the ''earlier of'' the estimated completion date or the actual completion date (79 FR 69632). Under proposed § 11.64(b)(1), however, responsible parties would be required to update the estimated completion date not later than 30 calendar days after a change to the estimated completion date has occurred or after the applicable clinical trial has reached its actual completion date. Therefore, submission 1 year after the actual completion date would then always reflect the ''earlier of'' 1 year after the estimated completion date or the actual completion date. Thus, under proposed § 11.44(a)(1), results information would be due not later than 1 year after the actual completion date of the applicable clinical trial. This proposed 1 year standard submission deadline would apply to applicable clinical trials of drugs and devices in order to simplify results information submission procedures and provide consistency between the deadlines for applicable clinical trials, regardless of the approval status of the products under study. Section 402(j)(3)(D)(iv)(III) of the PHS Act requires the Secretary to determine by regulation ''the date by which . . . clinical trial [results] information [for applicable clinical trials of unapproved, unlicensed, or uncleared products] shall be required to be submitted . . .'' Applicable clinical trials of unapproved, unlicensed, or uncleared drugs and devices, and of approved, licensed, or cleared drugs and devices that are studied for a new use may, however, qualify for delayed submission of results information, as described below. As we noted in the NPRM, although section 402(j)(3)(D)(iv)(I) of the PHS Act requires the Secretary to determine whether to increase the standard submission deadline for results information submission from 1 year to ''a period not to exceed 18 months'' after the earlier of the estimated or actual primary completion date, the Agency chose not to propose extending the general results information submission deadline to as long as 18 months (79 FR 69633).

Proposed § 11.44(a)(2) specified that the deadline for submitting results information for any applicable clinical trial of an FDA-regulated drug (including a biological product) or device that is unapproved, unlicensed, or uncleared as of its completion date would be by the earlier of 1 year after the completion date, or 30 calendar days after FDA approves, licenses, or clears the drug or device for any indication studied in the applicable clinical trial (79 FR 69633).

Comments and Response

Comments on proposed § 11.44 expressed different opinions. While one commenter expressed overall support for the proposal, others suggested modifications to various parts. Others raised concerns that the overall proposed submission and public posting timelines for trial results information could lead to premature dissemination of confidential commercial information, especially if posted prior to peer-reviewed publication or review by the FDA.

As we explained in the NPRM, we did not propose to require the submission of detailed information about clinical trial results (such as required for inclusion in an NDA submitted to FDA), but only summary results data typically found as tables or figures in journal articles, scientific abstracts, and press releases. As mandated by section 402(j)(3) of the PHS Act and established in the final rule § 11.48, responsible parties are required to submit at minimum a standard set of data elements needed to understand the findings from an applicable clinical trial for all prespecified primary and secondary outcome measures and serious adverse events in a structured manner. Further, results information submissions are required for all applicable clinical trials subject to the final rule according to deadlines established by the final rule, regardless of product approval status, to ensure consistent and timely public access to comprehensive summary results for all relevant clinical trials, thereby mitigating the prevalent problems of selective results reporting and negative results publication bias [Ref. 21, 22].

One commenter suggested that the results information submission time frames prescribed in the final rule should conform to those outlined in the 2015 IOM report on sharing clinical trial data [Ref. 47] to minimize the administrative burden on sponsors and responsible parties. Another commenter suggested that results information should be made available as it is created (*i.e.,* real time submission). The

requirements in the final rule are consistent with the Agency's authority in section 402(j) of the PHS Act and represent the Agency's determination, consistent with that authority, as to the appropriate results information submission deadlines for applicable clinical trials of unapproved products.

Regarding the standard results information submission deadline following initial approval, licensure, or clearance, described in proposed § 11.44(a)(2), one commenter recommended that, for applicable clinical trials of unapproved, unlicensed, or uncleared products for which the collection of pre-specified secondary outcome measures continues past the completion date, the standard results information submission deadline should be extended to the date of final data collection for all pre-specified secondary outcome measures (*i.e.,* at LPLV). The commenter also suggested that such a change would be consistent with results information submission deadlines established under the EU's Clinical Trials Regulation [Ref. 70]. Section 402(j)(D)(iv)(I) of the PHS Act authorizes the Agency to increase by regulation the standard results information submission deadline from 1 year following the completion date described in 402(j)(3)(E)(i) of the PHS Act ''to a period not to exceed 18 months.'' The statutorily-mandated definition of completion date (here referred to as primary completion date; see preamble Section IV.A.5 and § 11.10(a)) is determined by the status of data collection for solely the primary outcome measure(s), as is the basis for determining the standard results information submission deadline from the statutorily-mandated primary completion date. The final rule permits the responsible party to delay submission of results information for applicable clinical trials for up to 2 additional years by submitting a certification under § 11.44(b) if the manufacturer is the sponsor and is seeking approval, licensure, or clearance for a new use or under § 11.44(c) if the sponsor is seeking initial approval, licensure, or clearance. Such delays provide up to 2 additional years to complete data collection for pre-specified outcome measures and/or additional adverse event information.

Further, the final rule specifies timelines in § 11.44(d) for submitting partial results information by the date on which results information is due even if data collection for secondary outcome measure(s), or the pre-specified time frame for collecting additional adverse events information, has not been completed. These timelines provide submission deadlines for additional partial results information of not later than 1 year after the date on which final data collection for secondary outcome measure(s) or the pre-specified time frame for collecting additional adverse event information is completed, or on the date on which results information for primary outcome measure(s) is due following delayed certification, as specified in § 11.44(b) and (c). In addition, this approach ensures timely submission of results information for the primary outcome measure(s), but permits delays for the submission of other results information to allow time for the final collection and analysis of secondary outcome measure(s) and/or additional adverse event information. We note that, in situations in which the submission of results information for the primary outcome(s) of an applicable clinical trial would impair or otherwise bias the ongoing collection, analysis, and/or interpretation of data for secondary outcome(s) (*e.g.,* need to maintain masking in a trial), responsible parties may request an extension of the results information submission deadline for good cause by following the procedures specified in § 11.44(e).

A few other commenters suggested modifying proposed § 11.44(a)(2), which addressed results information submission for applicable clinical trials of products not approved, licensed, or cleared as of the completion date, but that receive FDA approval, licensure, or clearance thereafter. These commenters asserted that the proposal is inconsistent with the statutory language. In particular, they asserted the proposed regulatory language stating that results information submission is required ''by the earlier of'' (i) 1 year after the completion date or (ii) 30 calendar days after FDA approval, licensure, or clearance of the product contradicts section 402(j)(3)(E)(i) of the PHS Act, which states ''not later than 1 year, or such other period as may be provided by regulation.'' The commenters suggested that to be consistent with the statute, the standard results information submission deadline should be changed to ''by the later of'' in the final rule. As discussed in Section IV.F below, we have reconsidered the approach described in the NPRM (79 FR 69593) with respect to determining whether an applicable trial involves an approved, licensed, or cleared product, or whether it involves an unapproved, unlicensed, or uncleared product. For purposes of this final rule, the marketing status of a product will be determined based on its marketing status on the primary completion date. Thus, if a drug product (including a biological product) or a device product is approved, licensed, or cleared for any use as of the primary completion date, we will consider that applicable clinical trial to be a trial of an approved, licensed, or cleared product. Similarly, if a drug product (including a biological product) or a device product is unapproved, unlicensed, or uncleared for any use as of the primary completion date, regardless of whether it is later approved, licensed, or cleared, we will consider that applicable clinical trial to be a trial of an unapproved, unlicensed, or uncleared product. Furthermore, as noted in the preamble section discussing § 11.42(b) and in Section III.B Submission of Results Information for Applicable Clinical Trials of Unapproved, Unlicensed, or Uncleared Products for Any Use and Section IV.F. Effective Date, Compliance Date, and Applicability of Requirements in this Part, applicable clinical trials of an unapproved, unlicensed, or uncleared product are not subject to results information submission requirements until the effective date of the final rule. Thus, whether results information submission is required for an applicable clinical trial of an unapproved, unlicensed, or uncleared product depends on whether the primary completion date for that trial falls before, on, or after the effective date of the rule. Results information submission, therefore, is not required for applicable clinical trials of products not approved, licensed, or cleared for any use as of the primary completion date but receive FDA approval, licensure, or clearance thereafter when the primary completion date is before the effective date of the rule.

Other commenters suggested that results information submission should be required earlier than the proposed standard submission deadline (*i.e.,* earlier than 1 year after the completion date) whenever a responsible party publicly discloses results information for a clinical trial elsewhere, such as in a publication. Some commenters also suggested that the deadline for submission of results information in this circumstance should be 30 days after the date of public disclosure.

The Agency disagrees with the suggestion that we should make the date of any public disclosure of trial results a ''trigger'' for mandatory early results information submission. Sponsors and researchers publicly disclose trial results for many reasons, including compliance with other federal laws or policies (*e.g.,* disclosure requirements to the U.S. Securities and Exchange

Commission that may contain information about trial results). The final rule is consistent with section 402(j)(3)(E)(i) of the PHS Act, which provides up to 1 year from the completion date for results information submission. For the purpose of describing mandatory results information submission deadlines under this section, a triggering event refers to any of the events specified in paragraphs (b)(1)(i), (ii), and (iii) and paragraphs (c)(1)(i) and (ii) of this section that prompt results information submission for a clinical trial with a certification for delayed results information submission. The responsible party has 30 calendar days from the date of a triggering event to submit results information. We note that the definition of ''primary completion date'' in § 11.10(a) refers to the definition of ''completion date'' in § 11.10(a), which is ''for a clinical trial, including an applicable clinical trial, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated. In the case of clinical trials with more than one primary outcome measure with different primary completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes. For a pediatric postmarket surveillance of a device product that is not a clinical trial, completion date means the date on which the final report of the pediatric postmarket surveillance of the device product is submitted to FDA. For purposes of this part, completion date will be referred to as 'primary completion date.' '' In the case that data collection is completed for at least one primary outcome measure (but not yet for all primary outcome measures), clinical trial results information as specified in § 11.48(a) may be submitted before the primary completion date of the clinical trial.

Final Rule

Taking into consideration the commenters' suggestions and the statutory requirements for results information submission deadlines, the final rule modifies the approach proposed in § 11.44(a) by deleting proposed § 11.44(a)(2), which would have required results information submission for a clinical trial of a product that is unapproved, unlicensed, or uncleared for any use as of its completion date by the earlier of 1 year after the completion date or 30 calendar days after the date FDA approves, licenses, or clears the drug or device for any indication studied in the applicable clinical trial.

As noted above and discussed in Section IV.F on Effective Date, Compliance Date, and Applicability of Requirements in this Part, the Agency has reconsidered its approach with respect to determining whether an applicable clinical trial involves an approved, licensed, or cleared product, or whether it involves an unapproved, unlicensed, or uncleared product. For purposes of this final rule, the marketing status of a product will be determined based on its marketing status as of the primary completion date. With this approach, under section 402(j)(3)(C) of the PHS Act, results information submission is not required for clinical trials of a product that is unapproved, unlicensed, or uncleared for any indication as of its primary completion date where the primary completion is before the effective date. Further, as discussed in Section III.B Submission of Results Information for Applicable Clinical Trials of Unapproved, Unlicensed, or Uncleared Products for Any Use and Section IV.F Effective Date, Compliance Date, and Applicability of Requirements in this Part of the preamble, when the primary completion date is on or after the effective date of the final rule, the rule requires results information submission from applicable clinical trials of all products that were unapproved, unlicensed, or uncleared for any indication before the primary completion date. For trials of unapproved, unlicensed, or uncleared products completed after the effective date, results submission is generally required in accordance with the standard submission deadline. Thus, it is not necessary for final § 11.44(a) to contain separate subparagraphs to account for the approval, clearance, or licensure status of the product studied by the applicable clinical trial.

Final § 11.44(a) retains the proposed standard submission deadline of 1 year after the primary completion date regardless of product approval, clearance, or licensure status. We clarify that § 11.44(a) applies to applicable clinical trials subject to § 11.42 and that the results information required is specified in either sections 402(j)(3)(C) and 402(j)(3)(I) of the PHS Act or in § 11.48, as appropriate. As discussed in Section IV.F Effective Date, Compliance Date, and Applicability of Requirements in this Part, below, whether a responsible party is required to submit either results information specified in sections 402(j)(3)(C) and 402(j)(3)(I) of the PHS Act or the results information specified in § 11.48 will depend on whether the primary completion date of the applicable clinical trial is before, on, or after the effective date of the final rule.

§ 11.44(b) and (c)—Delayed Submission of Results Information With Certification

Overview of Proposal

Proposed § 11.44(b) and (c) established procedures whereby responsible parties may delay submission of results information for a particular applicable clinical trial beyond the standard submission deadline specified in proposed § 11.44(a)(1) (*i.e.,* 1 year after the completion date) (79 FR 69633).

Delayed Submission of Results Information With Certification If Seeking Approval, Licensure, or Clearance of a New Use

Consistent with sections 402(j)(3)(E)(iii) and (v) of the PHS Act, we proposed in § 11.44(b) to allow a delay in the submission of results information if the responsible party certifies that an applicable clinical trial meets the following criteria: (1) The drug (including biological product) or device studied in the applicable clinical trial previously has been approved, licensed, or cleared by FDA; (2) the sponsor of the applicable clinical trial is the manufacturer of the product; and, (3) the manufacturer has filed, or will file within 1 year, an application or premarket notification seeking approval, licensure, or clearance of the use being studied in the applicable clinical trial (and is not included in the labeling of the approved, licensed, or cleared drug or device). As proposed, the responsible party would need to submit this certification to *ClinicalTrials.gov* before the standard submission deadline specified in proposed § 11.44(a)(1) (*i.e.,* 1 year or less after the completion date). We also proposed to indicate on the posted record for the clinical trial that results submission has been delayed, but would not specify the particular reason for the delay (79 FR 69633).

As we explained in the NPRM, in accordance with section 402(j)(3)(E)(v) of the PHS Act, once a certification has been submitted to *ClinicalTrials.gov,* proposed § 11.44(b)(2) would permit a delay in the submission of results information of up to 2 years after the date on which the certification is submitted, unless one of the following events occurs: (1) FDA approves, licenses, or clears the drug or device for the use studied in the applicable clinical trial; (2) FDA issues a letter that

ends the regulatory review cycle for the application or submission (*e.g.,* a complete response letter, a not substantially equivalent letter, or a not approvable letter) but does not approve, license, or clear the drug or device for the use studied in the applicable clinical trial; or, (3) the manufacturer, which is also the sponsor of the applicable clinical trial, withdraws the application or premarket notification seeking approval, licensure, or clearance of the new use and does not resubmit it within 210 calendar days. In the event that any one of these triggering events occurs, the proposed rule said that the responsible party would be required to submit results information for the applicable clinical trial for which a certification had been submitted under proposed § 11.44(b)(1) not later than 30 calendar days after the earliest of the triggering events occurred, consistent with section 402(j)(3)(E)(v)(I) of the PHS Act (79 FR 69633).

As we noted, proposed § 11.44(b)(3) implemented section 402(j)(3)(E)(v)(II) of the PHS Act, which specifies that if a responsible party who is both the manufacturer of the drug or device studied in the applicable clinical trial and the sponsor of the applicable clinical trial submits a certification to delay submission of results information because the manufacturer is seeking or will seek within 1 year approval, licensure, or clearance of a new use for a drug or device, that responsible party must submit such a certification for each applicable clinical trial that meets the following criteria: (i) The applicable clinical trial is required to be submitted in an application or premarket notification for seeking approval, licensure, or clearance of a new use; and, (ii) the applicable clinical trial studies the same drug or device for the same use as studied in the applicable clinical trial for which the initial certification was submitted (79 FR 69633).

Delayed Submission of Results With Certification If Seeking Initial Approval, Licensure, or Clearance

Proposed § 11.44(c) described requirements for delayed submission of results information with certification when seeking initial approval, licensure, or clearance of a drug or device. As we explained in the NPRM, section 402(j)(3)(D)(iv)(III) of the PHS Act required that, when proposing to require the submission of results information for trials of unapproved, unlicensed, or uncleared products, we take into account the certification process in section 402(j)(3)(E)(iii) of the PHS Act ''when approval, licensure, or clearance is sought,'' and that we determine ''whether there should be a delay of submission when approval, licensure or clearance will not be sought'' (79 FR 69634).

We proposed in § 11.44(c) to allow a delay in the submission of results information if the responsible party certifies that an applicable clinical trial meets the following criteria: (1) The drug (including biological product) or device studied in the applicable clinical trial was not approved, licensed, or cleared by FDA for any use before the completion date of the clinical trial; and, (2) the sponsor of the applicable clinical trial intends to continue with product development and is seeking, or may at a future date seek, FDA approval, licensure, or clearance of the drug or device under study. As proposed, this certification would be required to be submitted to *ClinicalTrials.gov* before the standard submission deadline specified in proposed § 11.44(a)(1) (*i.e.,* 1 year or less after the completion date). The record for the clinical trial would indicate that results submission has been delayed, but would not specify the particular reason for the delay (79 FR 69634).

As proposed in § 11.44(c), submission of a certification would permit a delay in the submission of results information of up to 2 years after the date on which the certification is submitted to *ClinicalTrials.gov,* unless either of the following events occurs: (1) FDA approves, licenses, or clears the drug or device studied in the applicable clinical trial for any indication that is studied in the clinical trial; or, (2) the application or premarket notification is withdrawn without resubmission for not less than 210 calendar days. The responsible party would be required to submit results information not later than 30 calendar days after the one of these triggering events occurs. We explained that the Agency included the second event (*i.e.,* withdrawn without resubmission for not less than 210 calendar days) because we believe that this situation represents a significant enough interruption to product development to trigger the submission of results information. Unlike delayed results information submission with certification under proposed § 11.44(b), which applies when the sponsor (which is the manufacturer) of the applicable clinical trial is seeking approval, licensure, or clearance of a new use, we did not propose to require the submission of results information 30 calendar days after FDA issues a letter not approving, not licensing, or not clearing the product under study for delayed results information submission with certification seeking initial approval, licensure, or clearance because the issuance of such a letter does not necessarily indicate abandonment of product development (79 FR 69634).

Two-Year Limitation of Delay

As we discussed in the NPRM, with regard to the maximum 2-year delay pursuant to a certification submitted under section 402(j)(3)(E)(iii) of the PHS Act, we had considered establishing the maximum available delay with certification when seeking initial approval, licensure, or clearance to be 3 years from the completion date of the applicable clinical trial, regardless of when during the 1-year period following the completion date the certification is submitted. Such a provision would have accomplished the same objective as the statutory provision for delayed submission when seeking approval, licensure, or clearance of a new use by allowing responsible parties to delay results submission by as long as 3 years beyond the completion date of a clinical trial, but without creating a disincentive to submit the certification early. As we explained in the NPRM, measuring the 2-year period from the date on which the certification is submitted may result in responsible parties submitting certifications as close as possible to the standard results submission deadline under proposed § 11.44(a)(1) to obtain the full 3-year delay after the completion date. Section 402(j)(3)(D)(iv)(III) of the PHS Act expressly authorizes the Secretary to establish the date by which clinical trial information for applicable clinical trials of unapproved products must be submitted to *ClinicalTrials.gov*. Thus, in order to maintain the same maximum delay for results information submission whether seeking initial approval, licensure, or clearance or seeking approval, licensure, or clearance of a new use, we did not propose that the maximum 3-year delay apply regardless of when during the 1-year period following the completion date the certification is submitted. We invited public comments on establishing different maximum timelines for results information submission under the two delayed-results-with-certification provisions and on alternative approaches to encourage early submission of certifications that would be consistent with the statute, without causing a responsible party to have to submit results information earlier than the latest deadline they could have under the statute (79 FR 69635).

Explanation of ''initial approval,'' ''initial clearance,'' and ''approval of a new use,'' or clearance of a new use''

For purposes of proposed § 11.44(b) and (c), we interpreted the term ''drug'' in sections 402(j)(3)(E)(iv) and 402(j)(3)(E)(v) of the PHS Act to mean ''drug product'' or ''biological product,'' referring to a finished product that is approved or licensed for marketing, and not to the active ingredient or active moiety in such a product. We concluded that this is the most appropriate interpretation of the statutory term and that this interpretation is consistent with the statutory intent to draw a distinction between applicable drug clinical trials that are ''completed before the drug is initially approved'' (see section 402(j)(3)(E)(iv) of the PHS Act) and those pertaining to uses ''not included in the labeling of the approved drug'' (see section 402(j)(3)(E)(v) of the PHS Act). Accordingly, we interpreted ''initial approval'' to pertain to the approval or licensure of an original NDA, ANDA or BLA, and ''new use'' to pertain to the approval or licensure of a supplemental NDA, ANDA, or BLA for an additional use for that particular drug product or biological product. Similarly, we interpreted ''initial approval'' of a device under sections 515 or 520(m) of the FD&C Act to pertain to the approval of an original PMA or HDE and ''new use'' to pertain to the approval of a supplemental PMA for an additional use for that particular device. In addition, for purposes of proposed § 11.44(c), we considered the first 510(k) cleared for a particular device type as the ''initial clearance'' of the device. Consequently, for purposes of proposed § 11.44(b), all other 510(k)s cleared for a device type, other than the first one, would have been considered ''clearance of a new use.'' We solicited comments on whether these are appropriate interpretations and distinctions for purposes of proposed § 11.44(b) and (c) (79 FR 69635).

Comments and Response

Commenters addressed delayed submission of results with certification in proposed § 11.44(b) and (c). While one commenter supported the proposed delay of results submission for up to 2 years following the date of submission of a certification in proposed § 11.44(c), another commenter proposed simplifying the approach for calculating the deadline for this maximum delay by uniformly allowing up to 3 years after the primary completion date, regardless of when a certification is submitted. This commenter, however, did not explain how the statute allows for this proposed approach. As noted previously here and in the proposed rule, the statute does not permit changing by rulemaking when the 2-year maximum available delay for results submission would begin for submitted certifications seeking approval, licensure, or clearance of a new use for the studied drug or device. Section 402(j)(3)(E)(v)(III) of the PHS Act states that the time period begins on the date that the certification is submitted. While the statute provides greater flexibility for establishing the timelines for certifications seeking initial approval, licensure, or clearance for a studied drug or device, we have decided to keep the same approach for determining the maximum delay under both types of certifications, for reasons discussed in the NPRM. As such, the final rule retains the proposed approach (*i.e.,* ''not later than 2 years after the date on which the certification was submitted'').

One commenter proposed allowing an additional year to delay the submission of results for purposes of journal publication. Another commenter suggested that the Agency provide a new certification-like mechanism for delaying the submission of results of applicable clinical trials of approved, licensed, or cleared products for up to 2 years (as permitted for unapproved, unlicensed, or uncleared products) to allow academic researchers to prepare for journal publication. Several commenters proposed that the final rule routinely provide delayed submission of results for other reasons, such as publication prior to public posting on *ClinicalTrials.gov*. The statutory provision that pertains to delayed submission of results with certification is in section 402(j)(3)(D)(iv)(III) of the PHS Act, which explicitly directs the Agency to take into account during rulemaking the delayed submission of results with certification provisions when proposing to require the submission of results for applicable clinical trials of unapproved, unlicensed, or uncleared products, whether or not approval, licensure, or clearance is sought. In response to this mandate, the Agency proposed permitting delayed submission of results in proposed § 11.44(c) for applicable clinical trials of unapproved, unlicensed, or uncleared products undergoing product development. However, the NPRM proposed at § 11.44(a) to require the standard submission deadline for trials of unapproved, unlicensed, or uncleared products for which product development has been abandoned (see Section III.B of this preamble).

The Agency does not agree that submission of results information should be delayed for purposes of journal publication. Moreover, we note that the ICMJE clinical trial registration policy recognizes the results reporting obligations under section 402(j) of the PHS Act and states that ''the ICMJE will not consider results data posted in the tabular format required by *ClinicalTrials.gov* to be prior publication'' [Ref. 98]. Therefore, we do not expect that the requirements of the final rule for submission of results information will interfere with journal publication of articles about applicable clinical trials.

One commenter proposed requiring submission of results information for applicable device clinical trials only after the manufacturer has declared product development to be abandoned. This commenter noted further that receipt of an initial non-approval or not substantially equivalent finding from the FDA does not necessarily indicate that product development has stopped and suggested that the final rule provide for additional delays for results submission until the manufacturer has declared product development to be abandoned. As discussed in more detail in Section III.B of this preamble, the Agency has decided to maintain the requirement of results information submission for applicable clinical trials of drug and device products that are not approved, licensed, or cleared by the FDA for any use, regardless of whether approval, licensure, or clearance is sought. We continue to believe that this approach is consistent with the express statutory purpose of the expanded data bank ''[t]o provide more complete results information and to enhance patient access to and understanding of the results of clinical trials'' (see section 402(j)(3)(D)(i) of the PHS Act). As discussed previously, § 11.44(c) mitigates concerns about potential competitive harm resulting from disclosure of results information from applicable clinical trials of products that are not approved, licensed, or cleared by delaying the results submission deadline for applicable clinical trials of products that are still under development. Thus, we do not agree with commenters who suggested that results submission for applicable device clinical trials (or for applicable drug clinical trials) should be limited to trials of abandoned products. Consistent with section 402(j)(3)(E)(v)(I)(bb) of the PHS Act, § 11.44(b)(1)(ii) of the final rule provides that the issuance of a letter by the FDA including ''a complete response letter, not approving the

submission or not clearing the submission, a not approvable letter, or a not substantially equivalent letter for a new use of the drug or device'' that ends the regulatory review cycle for the application or submission but does not approve, license, or clear the product for the use studied in the applicable clinical trial, requires the responsible party to submit within 30 calendar days clinical trial results information for an applicable clinical trial, which had previously been subject to delayed submission of results information.

One commenter suggested that confidential commercial or proprietary information should not need to be submitted as part of the certification process. We clarify that to obtain a certification for delayed results information submission, a responsible party will need to indicate that a particular applicable clinical trial meets the requirement for delayed submission with certification in accordance with § 11.44(b) or (c) and provide the name(s) of the drug product(s), biological product(s), or device product(s), to which the certification applies. This information is necessary to demonstrate that the certification requirement has been met. No additional information will be required as part of this process.

One commenter suggested that we should post the reason a responsible party has been granted a certification for delayed results submission or extension. As noted above in the discussions of § 11.44(b) and (c), for applicable clinical trials that have been granted a certification for delayed results information submission or extension, the posted record will indicate only that the results information submission has been delayed but it will not specify the particular reason for the delay.

Finally, a few commenters disagreed with the Agency's interpretation that only the first 510(k) cleared for a particular device type be considered ''initial clearance.'' They asserted that every 510(k) clearance should be considered ''initial clearance,'' which would result in a potentially longer delay in submitting results information, rather than considered clearance of a ''new use'' because the trigger for submitting results information in proposed § 11.44(b)(1)(ii) is not found in proposed § 11.44(c). The commenters' arguments appear to be rooted in a concern that premature disclosure of clinical trial results information would enable competitors to shorten the time and expense to develop and market a similar device. The commenters' proposal would result in treating all 510(k) clearances as ''initial clearance'' under section 402(j)(3)(E)(iv) regardless of whether or not the 510(k) submission is an original submission by a manufacturer to obtain initial clearance of a device product as compared with a subsequent application by the same manufacturer to obtain clearance of the same device product for a different use. The Agency disagrees with the commenters' proposal because, by considering every 510(k) clearance to be an ''initial clearance'' under section 402(j)(3)(E)(iv) of the PHS Act, and considering no 510(k) clearances to be clearance of a ''new use'' under section 402(j)(3)(E)(v) of the PHS Act, such an interpretation would deprive section 402(j)(3)(E)(v) of the PHS Act of any meaning with respect to 510(k)s. Accordingly, the commenters' approach would contravene the principle of statutory construction that courts should give effect, if possible, to every clause and word of a statute, so as to avoid rendering any statutory language superfluous.

For NDA, ANDA, BLA, and PMA approvals, the NPRM focused on a manufacturer's particular ''product'' rather than on the ''type'' when determining whether a trial would be considered seeking ''initial approval,'' as specified in section 402(j)(3)(E)(iv), or ''approval of a new use,'' as specified in section 402(j)(3)(E)(v). In contrast, for 510(k)s, the NPRM focused on the device ''type'' rather than the device ''product'' for making such a determination. Under the NPRM, only the first 510(k) cleared for a device type was considered ''initial clearance'' and all other 510(k)s cleared for a device type were considered ''clearance of a new use.'' As a result, the NPRM approach resulted in disparate treatment of 510(k)s compared with the treatment of all other types of applications, including device PMAs.

To avoid disparate treatment of 510(k) submissions as compared with the treatment of all other types of applications, including PMA applications, in the final rule, the Agency is focusing on the device ''product'' rather than the device ''type'' when determining which 510(k) clearances are considered ''initial clearance'' versus ''clearance of a new use.'' That is, in the final rule, we interpret ''initial clearance'' to pertain to the clearance of a manufacturer's original 510(k) submission for a particular device product whereas ''clearance of a new use'' of a device pertains to the clearance of the same manufacturer's subsequent 510(k) submission for an additional use for the same device product. ''Manufacturer'' means a manufacturer who is the sponsor for the applicable clinical trial. The final rule, thus, treats 510(k)s in the same way it treats NDAs, ANDAs, BLAs, and PMAs by consistently basing its determination on the ''product'' rather than the ''type'' when determining whether a trial is seeking ''initial'' approval, licensure, or clearance, or approval, licensure, or clearance of a ''new use.'' This represents a middle-ground approach between the NPRM approach and the approach advocated by the commenters.

For the purposes of this final rule only, we interpret ''use'' to include ''indication.'' For the purposes of this final rule, ''indication'' means ''the disease or condition the product is intended to diagnose, treat, prevent, cure, or mitigate.''

Thus, for purposes of the final rule, the Agency interprets the first 510(k) clearance of a device ''product'' rather than the first 510(k) clearance of a device ''type'' as ''initial clearance'' under section 402(j)(3)(E)(iv) of the PHS Act. Any subsequent clearance of an ''initially cleared'' 510(k) device product for a different use will be considered a ''clearance of a new use'' under section 402(j)(3)(E)(v) of the PHS Act.

This interpretation in the final rule allows a responsible party for an applicable clinical trial of a 510(k) device product that is uncleared on the primary completion date to seek delayed submission of results information by submitting a certification that it is seeking ''initial clearance'' of its device product under § 11.44(c), rather than ''clearance of a new use'' under final § 11.44(b). With regard to FDA's issuance of a letter that ends the regulatory review cycle but does not approve, license, or clear the product for the use studied in the applicable clinical trial, as described in § 11.44(b)(1)(ii), we note, first, that it does *not* trigger results information submission within 30 calendar days of the event under § 11.44(c)(1) and, second, that there are *no* ''additional requirements'' in § 11.44(c) for responsible parties who are both the manufacturer of the product and the sponsor of the applicable clinical trial to submit certifications for each additional applicable clinical trial that studies the same product for the same use and is required to be submitted in a premarket notification for that use (as required in § 11.44(b)(3)).

We also note that this interpretation has implications for the registration requirements in the final rule because the concepts of ''initial clearance'' and ''clearance of a new use'' also appear in the registration provisions of the statute. This interpretation subjects clinical trial

registration information for more applicable clinical trials of unapproved or uncleared devices to delayed posting under section 402(j)(2)(D)(ii)(I) as compared with the NPRM approach because each individual device manufacturer seeking initial clearance of its device product would be subject to delayed posting of its clinical trial registration information, as specified in final § 11.35(b)(2)(i), rather than only the first manufacturer to obtain clearance for the device type. We note, however, that under final § 11.35(b)(2)(ii), a responsible party for an applicable device clinical trial that is initiated on or after the effective date of the rule may choose to indicate to the Director that it is authorizing the Director to publicly post its clinical trial registration information, that would otherwise be subject to delayed posting, as specified in § 11.35(b)(2)(i), prior to the date of FDA approval or clearance of the device product.

Final Rule

Final § 11.44(b)(1) retains the proposed procedure to allow a responsible party to delay results information submission with a certification indicating that the manufacturer, who is also the sponsor of the applicable clinical trial, is or will be seeking approval, licensure, or clearance of a new use for the studied drug product (including biological product) or device product, but clarifies that ''drug'' means ''drug product'' and ''device'' means ''device product.'' To obtain such a delay, the responsible party would need to submit a certification to *ClinicalTrials.gov* before the standard submission deadline specified in § 11.44(a) (*i.e.,* 1 year or less after the primary completion date). The responsible party would need to certify that (1) an applicable clinical trial involves an FDA-regulated drug product (including biological product) or device product that previously has been approved, licensed, or cleared by the FDA; (2) for which the manufacturer is the sponsor of the applicable clinical trial; and, (3) for which an application or premarket notification seeking FDA approval, licensure, or clearance of the use being studied in the applicable clinical trial, which is not included in the labeling of the approved, licensed, or cleared drug product (including a biological product) or device product, has been filed or will be filed within 1 year with FDA. The posted record for the applicable clinical trial would indicate that results information submission has been delayed, but would not specify the particular reason for the delay. For purposes of this part, we interpret ''manufacturer'' to mean a manufacturer who is the sponsor of the applicable clinical trial. Note that if the manufacturer designates a principal investigator as the responsible party as provided for at § 11.4(c)(2), the designated principal investigator would be required to submit the certification for delayed submission of clinical trial results information.

The deadline for the delayed submission of results information under § 11.44(b) would be 30 calendar days after the earliest of: (1) FDA approval, licensure, or clearance of the drug product (including a biological product) or device product for the use studied in the applicable clinical trial; (2) FDA issuance of a letter ending the regulatory review cycle for the application or submission without product approval, licensure, or clearance for the use studied in the applicable clinical trial (*e.g.,* a complete response letter, a not substantially equivalent letter, or a not approvable letter); or, (3) withdrawal of the application or premarket notification without resubmission within 210 calendar days (*i.e.,* 240 calendar days after submission of the withdrawal request). Final § 11.44(b)(2) provides a maximum deadline for delayed results information submission of 2 years after the date of submission of the certification, except to the extent that § 11.44(d) applies. Final § 11.44(b)(3) provides an additional requirement that any responsible party who is both the manufacturer of the drug product (including a biological product) or device product studied and the sponsor of an applicable clinical trial, and who submits a certification for the delayed submission of results under § 11.44(b)(1) for that applicable clinical trial, must also submit such a certification for each applicable clinical trial for which the manufacturer of the drug product (including a biological product) or device product studied is the sponsor and which is required to be submitted in an application or premarket notification seeking approval, licensure, or clearance of a new use studied in the clinical trial.

We note that if the sponsor of an applicable clinical trial for which a ''new use certification'' has been submitted is also the manufacturer the drug product (including a biological product) or device product studied in the applicable clinical trial, but has designated the principal investigator as the responsible party, then the manufacturer may need to notify the responsible party of the occurrence of a triggering event in order to help ensure that the responsible party is aware of the results information submission deadline. As discussed in § 11.4(c)(2)(i) (see Section IV.A.2 of this preamble), the sponsor may designate a principal investigator as the responsible party only if, among other things, the principal investigator ''[h]as the ability to meet all of the requirements for submitting and updating clinical trial information as specified in this part.'' Accordingly, a responsible party who is not the manufacturer of the drug product (including a biological product) or device product studied will only be able to comply with the results information submission requirements subsequent to a certification under sections 402(j)(3)(E)(iii) and (v) if notified by the manufacturer when one of these triggering events occurs. If a manufacturer is not willing or able to provide the principal investigator with this information, the conditions for designation under § 11.4(c)(2) cannot be met and the manufacturer would become the responsible party until the manufacturer assigns a new responsible party (see § 11.4(c)(3)).

We also note that the maximum delay of 2 years specified in § 11.44(b)(2) would apply to clinical trial results information specified in sections 402(j)(3)(C) and 402(j)(3)(I) of the PHS Act or § 11.48, as applicable. With respect to applicable clinical trials for which data collection for any secondary outcome measures and/or additional adverse event information extends beyond the primary completion date, the deadlines for submission of these clinical trial results information are discussed under final § 11.44(d).

We recognize that in some cases a responsible party may not know whether a particular applicable clinical trial will be used to support an original NDA, ANDA, BLA, PMA, or HDE for initial approval or licensure of a product as opposed to a supplemental NDA, ANDA, BLA, or PMA for approval or licensure of a new use. Similarly, a responsible party may not know whether a clinical trial will be used to support a 510(k) seeking ''initial clearance'' of a device product as opposed to a 510(k) seeking ''clearance of a new use.'' Responsible parties should use their best judgment based on information available at the time of certification in order to determine whether certification under § 11.44(c) (initial approval, licensure, or clearance) or § 11.44(b) (approval, licensure, or clearance of a new use) is appropriate.

As discussed above, the Agency interprets ''initial clearance'' in the final rule to apply to the clearance of a manufacturer's original 510(k) submission for a device product for purposes of this part and any

subsequent clearance of that device product by that manufacturer for a different use would be considered ''clearance of a new use.'' By making this change, the final rule focuses on the device product, rather than the device type, to determine whether an applicable clinical trial of a 510(k) device will be considered as seeking ''initial clearance'' versus ''clearance of a new use.'' This means that under the final rule, 510(k) device product trials will be considered not by whether the type of device has ever been cleared before, but by whether the particular manufacturer's device product has ever been cleared.

Final § 11.44(c)(1) retains the proposed procedure to allow a responsible party to delay results information submission with a certification indicating that the sponsor is seeking initial approval, licensure, or clearance for the drug product (including a biological product) or device product, but clarifies that ''drug'' means ''drug product'' and ''device'' means ''device product.'' To obtain such a delay, the responsible party will need to submit a certification to *ClinicalTrials.gov* before the standard deadline specified in proposed § 11.44(a) (*i.e.,* 1 year or less after the primary completion date). The responsible party would need to certify that an applicable clinical trial (1) studies a drug product (including a biological product) or device product that was not approved, licensed, or cleared by FDA for any use before the primary completion date of the clinical trial; and, (2) the sponsor of the applicable clinical trial intends to continue product development and is seeking or intends to seek FDA approval, licensure, or clearance of the drug product (including a biological product) or device product under study. Certifications cannot be submitted for applicable clinical trials of products that the sponsor has no intention of marketing or for which product development has been abandoned.

When a certification for delay is submitted, the posted record for the clinical trial will indicate that results information submission has been delayed, but will not specify the particular reason for the delay. The deadline for delayed submission of results information under § 11.44(c) will be 30 calendar days after the earlier of: (1) FDA approval, licensure, or clearance of the drug product (including a biological product) or device product for the use studied in the applicable clinical trial; or, (2) withdrawal of the application or premarket notification by the sponsor of the applicable clinical trial without resubmission within 210 calendar days (*i.e.,* 240 calendar days after submission of the withdrawal request). We believe that this latter situation represents a significant enough interruption to product development to trigger the submission of results information. Final § 11.44(c)(2) retains a maximum deadline for delayed results information submission of 2 years after the date of certification submission. The Agency expects that a delay of an additional 2 years beyond the date the certification is submitted (*i.e.,* up to 3 years after the primary completion date of the clinical trial, assuming that the certification is submitted 1 year after the primary completion date) is sufficient to address any confidentiality concerns that may be expressed by responsible parties. This time frame allows a sponsor or manufacturer to decide whether to initiate another clinical trial or submit a marketing application or premarket notification to the FDA. A subsequent pre-market clinical trial of a drug product (including a biological product) would likely be an applicable clinical trial that would be registered at *ClinicalTrials.gov,* making public information about the sponsor's intention to pursue product development. Thus, the total delay in disclosure of results information of up to 3 years after the completion date of the trial would provide sponsors with significant lead time in product development over potential competitors. As discussed further in Section III.B of this preamble, we conclude that any competitive disadvantage that may be caused by the disclosure of summary results information for clinical trials of products that have not been approved, licensed, or cleared for any use 3 years or more after the primary completion date of the trial is limited and, in any case, outweighed by the public health benefits of making such information publicly available. Furthermore, as discussed above, even if such summary results information were to contain trade secret and/or confidential commercial information, the requirement that such information be posted on *ClinicalTrials.gov* is authorized by law for the purposes of the U.S. TSA.

Section 11.44(c) permits delayed submission of results information only if the responsible party certifies that the sponsor of the applicable clinical trial is continuing to study the product with an expectation of seeking future initial approval, licensure, or clearance. While we recognize it may be difficult for the sponsor of the applicable clinical trial to know early on in the product development process whether it will seek future initial approval, licensure, or clearance for a product studied in an applicable clinical trial, we would, in general, view further development of a product through subsequent clinical trials as an indication that the product development process is continuing and may lead to seeking initial approval, licensure, or clearance. A responsible party who is not the sponsor of the applicable clinical trial cannot submit a certification to delay results information submission unless the responsible party can obtain such information from the sponsor. If a principal investigator who has been designated as the responsible party by the sponsor cannot obtain such information, then the conditions for designation under § 11.4(c)(2) cannot be met and the responsible party will not be able to submit a certification for delayed results information submission. If a triggering event occurs, the responsible party who is not the sponsor (*i.e.,* a responsible party who is a principal investigator) will only be able to comply with the results information submission requirements under § 11.44(c)(2) if notified by the sponsor. In a situation in which the sponsor is not willing or able to provide the principal investigator with this information, the conditions for designation under § 11.4(c)(2) cannot be met and the responsible party will not be able to submit a certification for delayed results information submission.

As discussed with respect to § 11.44(b)(2), the maximum delay of 2 years specified in § 11.44(c)(2) would apply to clinical trial results information specified in § 11.48. In the event that data collection for any secondary outcome measure(s) will not be completed as of the primary completion date of the trial or the time frame for additional adverse event collection extends beyond the primary completion date, clinical trial results information for such secondary outcome measure(s) and additional adverse events information shall be due by the later of (1) the deadline for delayed submission of results with certification established by either final § 11.44(b) or (c) or (2) the submitting partial results deadlines established in final § 11.44(d)(1).

We also note that after a certification for delayed results information submission has been submitted under either § 11.44(b) or (c) for an applicable clinical trial, the final rule does not permit submission of an additional certification under § 11.44(b) to extend the results information submission deadline established by the existing certification for the same trial (see

§ 11.44(c)(2)). For example, a responsible party who has submitted a certification seeking ''initial approval'' under § 11.44(c) must submit results information by the earlier of 30 calendar days of the first triggering regulatory event (§ 11.44(c)(1)) or 2 years after the date of certification (§ 11.44(c)(2)), and cannot submit a certification seeking ''approval of a new use'' for that same trial, even if it studied both uses. Similarly, a responsible party who has submitted a certification seeking approval of a ''new use'' under § 11.44(b) must submit results information by the earlier of 30 calendar days of the first event described (§ 11.44(b)(1)) or 2 years after the date of certification (§ 11.44(b)(2)), and cannot submit another certification seeking approval of a ''new use'' for the same trial. We note that in certain situations, as discussed below in this section of the preamble, a responsible party may be able to request an extension for good cause under § 11.44(e).

§ 11.44(d)—Submitting Partial Results Information

Overview of Proposal

Proposed § 11.44(d) specified procedures for submitting results information when required results information, as specified in proposed § 11.48, has not been collected for all secondary outcome measures by the date on which results information is due. Since the definition of completion date in proposed § 11.10(a) is determined by the status of data collection solely for the primary outcome measure(s), an applicable clinical trial may therefore still be collecting data for the secondary outcome measure(s) after it has reached its completion date. In this situation, the responsible party would be required to submit results information for the primary outcome measure(s) by the required due date specified in proposed § 11.44(a), (b), or (c), as applicable. Under proposed § 11.44(d)(1)(i), if a certification to delay results information submission had not been submitted under proposed § 11.44(b) or (c), results information for each remaining secondary outcome measure would be due not later than 1 year after the date on which the final subject is examined or receives an intervention for the purposes of final collection of data for that secondary outcome measure, whether the clinical trial was concluded according to the pre-specified protocol or was terminated. If the responsible party had submitted a certification to delay results information submission, results information for the secondary outcome measures could be submitted by the later of the date specified in proposed § 11.44(d)(1)(i) or the date on which the primary outcome measure(s) would be required to be submitted under proposed § 11.44(b) or (c) as specified in proposed § 11.44(d)(1)(ii). We noted that in either situation, if data collection for a secondary outcome measure is completed as of the completion date, results information for that secondary outcome measure would be required to be submitted on the same date as results information for the primary outcome measure(s) (79 FR 69635).

We also clarified in proposed § 11.44(d)(2) the process to handle results information submission if results information related to the primary outcome(s) was submitted prior to the effective date of the final rule, but results information for the secondary outcome(s) is required to be submitted after the effective date. In such cases, the responsible party would be required to provide results information for all primary and secondary outcome(s) as specified in § 11.48 of the proposed rule. We indicated that, because we believe consistent data must be provided for all outcome measures in a single clinical trial, the requirements of proposed § 11.48 would apply to all clinical trial results information submitted for a trial (79 FR 69636).

With respect to adverse event information, considered to be part of clinical trial results information described under proposed § 11.48, a responsible party would be required to submit information summarizing serious and frequent adverse events recorded to-date each time results information for a secondary outcome is submitted until all the adverse event information required by this part has been submitted. We indicated that we believe such an approach would provide a better mechanism for handling submission of adverse event information than extending the general results submission deadline for all applicable clinical trials up to 18 months after the completion date. It would ensure that key results information for primary outcome measures is submitted to *ClinicalTrials.gov* within 1 year of the completion date, while allowing subsequent data collection to continue as planned (79 FR 69636).

Comments and Response

Commenters addressed § 11.44(d). One commenter suggested that the final rule require the submission of data for additional adverse event information on an annual basis, rather than during each deadline for the submission of partial results information involving secondary outcomes for which data collection was incomplete by the completion date. The Agency believes that requiring additional adverse event information data to be submitted annually rather than by the proposed partial results deadlines would potentially be more burdensome for responsible parties with few benefits for the public. For example, if a study protocol pre-specified time frames for both a secondary outcome measure and adverse events collection 5 years after the completion date, under the approach proposed in § 11.44(d), the responsible party would only need to submit results information once for the secondary outcome measure as well as data for additional adverse event information not later than 1 year after the date of final data collection (*i.e.,* up to 6 years after the completion date). Under the approach proposed by the commenter, however, that responsible party would also need to submit four datasets of additional adverse event information for this trial, once per year after the completion date until submission of results for the secondary outcome measure. In addition, protocols might not pre-specify that data for adverse event information will be analyzed annually, placing additional burden on the responsible party to prepare adverse event information for submission to the data bank. Thus, the Agency retains the proposed approach with respect to submission of adverse event information each time results information for a secondary outcome is submitted and extends the requirement until all additional adverse event information collected in accordance with the time frame for collecting adverse events pre-specified in the protocol are submitted, even after submission of data for all secondary outcomes.

Reporting of adverse event information is required as part of § 11.48(a)(4), yet the time frame for reporting of partial adverse event information was not specified in proposed § 11.44(d). After reviewing proposed § 11.44(d) in response to this comment, we identified the need to specify explicitly the deadline for submitting partial results information when the pre-specified time frame for collecting data for additional adverse event information is not completed by the primary completion date. We clarify that the final rule addresses this situation by specifying that a responsible party submitting partial results information under § 11.44(d) must submit additional adverse event

information by the later of either 1 year after the date of data collection for additional adverse event information or the date on which results information for the primary outcome measures is due if a certification to delay results information submission has been submitted under § 11.44(b) or (c). Further, we have added the Study Completion Date data element, defined in final § 11.10 and discussed in Section IV.A.5 of this preamble, to clinical trial registration information specified in § 11.28.

The Study Completion Date is needed to assist responsible parties and viewers of the posted record to help identify when the final rule requirements for results information submission and obligations for updates and corrections in § 11.64 are fulfilled. Note that even though a responsible party for a trial may need to submit partial results information several times in order to meet different deadlines (*i.e.,* because of different dates for final data collection for primary and/or secondary outcome measures or for the pre-specified time frame for collecting adverse events), that responsible party's obligation under subpart C continues until all required results information is submitted not later than 1 year following the Study Completion Date.

Several additional commenters opposed proposed § 11.44(d)(2), which required that results for primary and secondary outcomes submitted prior to the effective date of the final rule be resubmitted in accordance with final § 11.48 by the deadline for reporting partial results information for secondary outcome measures specified in proposed § 11.44(d)(1). The Agency agrees with these comments. The final rule specifies that if any results information is submitted for a clinical trial under sections 402(j)(3)(C) and 402(j)(3)(I) of the PHS Act prior to the effective date, those results do *not* need to be resubmitted in accordance with final § 11.48. In addition, partial results submitted for that trial after the effective date are also not subject to § 11.48 of the final rule, but are subject to the results data elements established by sections 402(j)(3)(C) and 402(j)(3)(I) of the PHS Act, in order to ensure that results data are displayed in a consistent format on the posted record.

Final Rule

The final rule substantively revises the proposed approach to § 11.44(d) in three ways. First, final § 11.44(d)(1)(ii) adds a partial results information submission deadline when adverse event information required in § 11.48(a)(4) has not been collected by the primary completion date. Under the final rule, data collected for additional adverse event information after the primary completion date through the pre-specified adverse event collection time frame must be submitted by the later of 1 year after the date of data collection for additional adverse event information or the date on which results information is due if a certification to delay results information submission has been submitted under § 11.44(b) or (c). Second, the final rule modifies § 11.44(d)(2) to specify that, if any partial results information for a clinical trial is submitted prior to the effective date of the final rule, any remaining results information required to be submitted for that trial after the effective date will be subject to the results requirements established by sections 402(j)(3)(C) and 402(j)(3)(I) of the PHS Act [42 U.S.C. 282(j)(3)(C) and 282(j)(3)(I)], not by the final rule (§ 11.48). Third, the final rule adds § 11.44(d)(3) to require (i) the submission of a copy of any revised protocol and/or statistical analysis plan, as described in § 11.48(a)(5), if any amendments were made to the protocol and/or statistical analysis plan since the previous submission of partial results information and (ii) the submission of results information about certain agreements between the principal investigator and the sponsor as described in § 11.48(a)(6)(ii) if that information has changed since the previous submission of partial results information.

Final § 11.44(d)(1) describes the partial results information submission deadlines when all clinical trial results information required in § 11.48 has not been collected by the primary completion date. In such cases, results information for secondary outcome measures must be submitted by the later of 1 year after the date on which the final subject is examined or receives an intervention for the purposes of final collection of data for that secondary outcome measure or the date on which results information is due if a certification to delay results information submission has been submitted under § 11.44(b) or (c). Furthermore, as discussed above, data collected for additional adverse event information after the primary completion date through the pre-specified adverse event collection time frame must be submitted by the later of 1 year after the date of data collection for additional adverse event information or the date on which results information is due if a certification to delay results information submission has been submitted under § 11.44(b) or (c).

We clarify that when submitting partial results information (pending completion of data collection for secondary outcomes and/or the pre-specified time frame for collecting additional adverse event information), the responsible party is required to submit the clinical trial results information as specified in § 11.48 that is otherwise available when submitting partial results information. This means that, with respect to adverse event information (considered to be part of clinical trial results information described under § 11.48), each time results information for a secondary outcome is submitted, a responsible party would be required to submit results information summarizing serious and frequent adverse events and all-cause mortality recorded to that date until all the adverse event information required by this part has been submitted. If adverse event information was not planned to be collected and reported in the same time frame(s) as secondary outcome measures, then it does not need to be reported each time information for a secondary outcome measure(s) is submitted. However, as specified in § 11.48(a)(4)(i)(A), the Time Frame must clearly indicate the time period over which adverse information is reported and describe any additional time periods over which adverse event information will be submitted, as pre-specified. It is important to reiterate that this provision would not impose requirements on the design or conduct of the clinical trial or on the data that must be collected during the clinical trial.

Final § 11.44(d)(2) specifies that if any results information is submitted for a clinical trial under sections 402(j)(3)(C) and 402(j)(3)(I) of the PHS Act prior to the effective date, the responsible party is not required to resubmit those results in accordance with § 11.48. In addition, subsequent partial results information as specified in § 11.44(d)(1) submitted for the same trial after the effective date is also not required to be submitted in accordance with final § 11.48, but in accordance with the results data elements established by sections 402(j)(3)(C) and 402(j)(3)(I) of the PHS Act. Final § 11.44(d)(3)(i) specifies that the responsible party is required to also submit a copy of the revised protocol and/or statistical analysis plan when submitting partial results information if the protocol and/or statistical analysis plan was amended since the previous submission of partial results information for that clinical trial. Final § 11.44(d)(3)(ii) specifies that the

responsible party is required to submit information to reflect any changes in the status of certain agreements between the principal investigator and the sponsor if that information has changed since the previous submission of partial clinical trial results information.

§ 11.44(e)—Extensions for Good Cause

Overview of Proposal

Proposed § 11.44(e) outlined procedures for requesting extensions of the deadline for submitting results information for good cause. Section 402(j)(3)(E)(vi) of the PHS Act authorizes the Director to ''provide an extension of the deadline for submission of clinical trial [results] information . . . if the responsible party for the trial submits to the Director a written request that demonstrates good cause for the extension and provides an estimate of the date on which the information will be submitted.'' We interpreted this authority as allowing the Director to grant an extension of any results information submission deadline that may be in effect for a given applicable clinical trial specified in proposed subpart C (*e.g.,* the general 12 month results information submission deadline); a delayed submission deadline established by the submission of an appropriate certification under section 402(j)(3)(E)(iii) of the PHS Act; or an extended deadline established by a previously granted extension. As for the latter, section 402(j)(3)(E)(vi) of the PHS Act explicitly allows the Director to ''grant more than one extension for a clinical trial.'' (79 FR 69636)

Section 402(j)(3)(E)(vi) of the PHS Act does not define ''good cause.'' Similarly, the proposed rule did not contain specific proposals for determining which situations would and would not be considered good cause for an extension. Instead, we indicated our intention to develop guidance (which would be subject to public comment) as the Agency gained more experience with extension requests and to communicate with the regulated community via other channels, including the *ClinicalTrials.gov* Web site. We intend to issue guidance on what might be considered ''good cause'' under particular circumstances as soon as practicable. In order to assist responsible parties who are considering submitting an extension request, we stated our intention to prepare, update periodically, and post on *ClinicalTrials.gov* a non-exhaustive list of reasons that the Agency generally will consider to be ''good cause'' and not ''good cause'' for granting an extension under section 402(j)(3)(E)(vi) of the PHS Act and proposed § 11.44(e). Such a list would contain those reasons that we consider would serve as useful examples for responsible parties of other applicable clinical trials. We also indicated that all extension requests would be considered on a case-by-case basis, and any generalizable conclusions that can be drawn from the granting or denial of a request may be added to the list of good causes and not-good causes for granting extensions (79 FR 69636).

In general, we indicated that there are likely to be only a few situations that would constitute good cause under section 402(j)(3)(E)(vi) of the PHS Act and proposed § 11.44(e) and listed the two situations that we have identified to date that we proposed would constitute good cause:

(1) The need to preserve the scientific integrity of an applicable clinical trial for which data collection is ongoing, including situations in which the submission of results information for the primary outcome(s) of an applicable clinical trial would impair or otherwise bias the ongoing collection, analysis, and/or interpretation of data for secondary outcome(s). We indicated our belief that an extension should be granted only in those situations in which the following could be demonstrated: Data collection for the secondary outcome(s) of interest extends more than 1 year beyond the completion date, the secondary outcome(s) is pre-specified in the protocol or SAP, and the planned analysis of the outcome measure is also described in the protocol or SAP. We noted that the responsible party could provide this information either by voluntarily submitting copies of the protocol or statistical analysis plan with the extension request or describing them in the extension request itself.

(2) Emergencies that would prevent timely submission of clinical trial results information, including situations in which one or more data collection sites were affected by natural disasters or other catastrophes outside the responsible party's or sponsor's control. In such cases, we indicated that we would generally expect to grant the responsible party an initial extension of up to 6 months, after which time additional extensions could be granted, as necessary. We generally would not consider events that might reasonably have been avoided or anticipated through standard contingency planning (*e.g.,* transition planning for key staff members who leave an organization) to constitute good cause for an extension under section 402(j)(3)(E)(vi) of the PHS Act or proposed § 11.44(e) (79 FR 69637).

To clarify what we believed would not ordinarily constitute good cause, we discussed two scenarios in the proposed rule's preamble. First we pointed out that a request containing only a general statement without any specific reason for a delay in data analysis (*e.g.,* ''data could not be analyzed fully within 12 months'') would not be a good cause. Second, we indicated that ''awaiting journal publication'' would not constitute a good cause. We noted that the ICMJE has stated that results information submission to *ClinicalTrials.gov* in compliance with section 402(j) of the PHS Act will not be considered ''prior publication'' and will not preclude future publication [Ref. 2, 98]. We invited public comment on these specific situations and on more general criteria that could be used to determine what constitutes good cause for an extension (79 FR 69637).

Proposed § 11.44(e)(1) specified that a responsible party may submit a request for an extension to *ClinicalTrials.gov* at any time before any results information submission deadline established in proposed § 11.44(a), (b), or (c), if the relevant certification has been submitted; or § 11.44(f), for a pediatric postmarket surveillance of a device that is not a clinical trial. Consistent with section 402(j)(3)(E)(vi) of the PHS Act, our proposal would require an extension request to include a complete description of the reason(s) why results information cannot be provided according to the applicable deadline and an estimated date on which results information will be submitted. The submitted extension request would be reviewed by an Agency official designated by the Director (79 FR 69637).

Proposed § 11.44(e)(2) indicated that the Agency would notify the responsible party electronically whether the request has been granted and, if granted, the Agency-specified extended deadline by which results information must be submitted. If the extension request is denied, the responsible party may either submit an appeal to the Director or would submit results information by the later of the original deadline or 15 calendar days after the date the Agency sends the electronic notice of the denial to the responsible party (79 FR 69637).

Proposed § 11.44(e)(3) specified that a responsible party may appeal a denied extension request or the Agency-specified extended deadline by which results information must be submitted not later than 15 calendar days after the date the Agency sends the electronic notice of the denial. Responsible parties are required to submit a description of the reasons for the appeal with

sufficient detail to allow for evaluation. If the appeal is granted, the responsible party must submit results information by the revised deadline set by the Director in the electronic notification. If the appeal is denied, the responsible party must submit results information by the later of the following: The original deadline, the Agency-specified extended deadline provided in the electronic notification, or 15 calendar days after the date the Agency sends the electronic notice of denial of the appeal to the responsible party (79 FR 69637).

We also noted that extensions would apply only in the context of applicable clinical trials subject to the results information submission requirements of section 402(j)(3) of the PHS Act because the extension provision specifically refers to results information submission under 402(j)(3)(E)(i) of the PHS Act. Accordingly, extensions do not apply to clinical trial results information that is submitted under section 402(j)(4)(A) of the PHS Act (*i.e.,* voluntarily submitted trials (see final rule § 11.60(a)(1)) and triggered trials (see final rule § 11.60(a)(2)(ii))) (79 FR 69636).

Posting of Information About Certifications for Delayed Submission and About Extensions for Good Cause

In the proposed rule, we suggested that there would be value in posting information on the *ClinicalTrials.gov* Web site about the specific mechanism that had been used to delay the submission of clinical trial results information for a particular applicable clinical trial (*i.e.,* an extension request had been granted under proposed § 11.44(e) or the responsible party had submitted a certification for delayed submission, specifying either proposed § 11.44(b) or (c)). Doing so would provide a way to track the progress of clinical trials by informing users why clinical trial results information is not yet publicly available. Without such an indication, users who view a posted clinical trial record that contains no results information more than 1 year after the primary completion date might be led to believe, incorrectly, that the responsible party has not complied with the results information submission requirements of this proposed rule or that the Agency has failed to post such information. However, we recognized that information about the specific mechanism used to delay results information submission might in some circumstances be considered confidential (*e.g.,* the fact that the manufacturer had submitted or was planning to submit within 1 year a marketing application or premarket notification to FDA for a new use of a drug or device that was studied in the applicable clinical trial prior to any public statement by the or manufacturer about its plans).

In order to balance the competing interests, we proposed posting only minimal information about delayed results information submissions in these circumstances. That is, whether a responsible party delayed results information submission via certification or is granted an extension of the deadline, we would indicate in the posted record only that results information submission has been delayed, but not which mechanism had been used. As described previously, we proposed posting and updating periodically on the *ClinicalTrials.gov* Web site a generalized list of reasons for which extensions have and have not been granted (without information that might allow a user to identify a specific applicable clinical trial) to provide responsible parties with insight into the types of reasons that have and have not been considered to constitute good cause for an extension (79 FR 69638).

We invited public comments on our overall proposed approach and on the advantages and disadvantages of providing more specific information about extension requests (*e.g.,* whether submission was delayed via extension or certification), including alternative approaches that we could take that would provide more information to the public about the reasons for delayed submissions of clinical trial results information. We also invited public comment on whether extension requests could be submitted without containing any information that would be considered confidential (79 FR 69638).

Comments and Response

Commenters addressed the proposed approach for implementing extensions of the results information submission deadline in § 11.44(e). One commenter suggested that 15 calendar days do not provide sufficient time for a responsible party either to submit a written letter to appeal a denial for an extension request or to submit results information following notification that an appeal has been denied as proposed in § 11.44(e)(3)(i) and (vi), respectively. We note that several other commenters requested more broadly that the 15 calendar day deadlines proposed in the proposed rule be changed to 30 calendar day deadlines in the final rule (see discussion of § 11.64 in Section IV.D.3 of this preamble). The Agency generally agrees with the commenters and has changed, where possible, the 15 calendar day deadlines in the proposed rule to 30 calendar day deadlines in the final rule (see Section IV.D.3 of this preamble).

One commenter requested clarification that extension requests are not subject to any limitations in time, in contrast to the 2-year limitation for delayed submission of results with certification as specified in proposed § 11.44(b)(2) and (c)(2). We clarify that requests for extensions of the results information submission deadline are not subject to a time limit and may include estimated submission dates over 2 years after the date of the request. However, all submitted requests must provide a sufficient description of the reason(s) for proposing the particular estimated submission date. We also note that, because the statute and final rule permit the Director to grant more than one extension, a final extended results information submission deadline may exceed more than 2 years, even if the initial extension did not.

Several commenters suggested additional good cause reasons, such as for trials of device products that have received either a non-substantially equivalent or non-approval letter from the FDA, for preparation and analysis of data from large and complex trials, and for pending publication of trial results. One commenter requested clarification regarding the circumstances under which a sponsor of an applicable clinical trial of an unapproved, unlicensed, or uncleared product could request an extension. Another commenter proposed limiting the situations that would be considered ''good cause'' to national emergencies or catastrophic events. As stated in the proposed rule and this preamble, the Agency plans to prepare and periodically update a public, non-exhaustive list of reasons that it considers to be ''good cause'' and ''not good cause.'' At present, we have identified only two general situations that we believe would constitute good cause: (1) The need to preserve the scientific integrity of a trial; and, (2) emergencies outside the control of a responsible party that would prevent timely submission, such as natural disasters or other catastrophes. In addition, we reiterate that we generally believe that pending publication and delays in data analysis for unspecified causes would not be considered good cause. We also note that requests for good cause may be submitted to extend any type of results information submission deadline, including the standard submission deadlines in § 11.44(a) (*i.e.,* 1 year after the primary completion date).

One commenter proposed that responsible parties submitting requests

for extensions not be required to include confidential commercial or proprietary information. This commenter also requested that *ClinicalTrials.gov* provide a way for the public to distinguish between applicable clinical trials with missing results submissions because of missed regulatory deadlines (*i.e.,* late submissions) and those for which an extension has been granted, as required in § 11.44(e). Although we do not believe that confidential commercial or proprietary information will generally need to be submitted, the responsible party must provide in a submitted request for an extension ''sufficient detail to allow for the evaluation of the request'' as stated in final § 11.44(e)(1)(ii)(A). The Agency will not post detailed information about the request publicly and retains its plan to post minimal information on posted records to notify users when results information submission has been delayed without specifying whether a certification or extension mechanism was used. The Agency believes this approach will provide sufficient and appropriate information to the public to explain the reason for delay (see discussion above on § 11.44(b), (c), and (e)).

One commenter suggested that the final rule provide members of the public, including third-party researchers, the ability to appeal any reasons given for delaying the submission of results and that any such appeals be made publicly available with contact information. The Agency does not agree with this approach. We do plan, as proposed, to post publicly a list of general reasons provided in requests for extensions which the Agency considers to be ''good cause'' and ''not good cause.''

Regarding the proposal to post on *ClinicalTrials.gov* a list of general reasons the Agency will consider to be ''good cause'' and ''not good cause'' for granting extensions, one commenter requested that the actual reasons cited in extension requests submitted by responsible parties not be posted while two other commenters suggested that all submitted justifications and estimated submission dates be posted publicly for greater transparency. Another commenter proposed requiring the posting of submitted information for extension requests no later than 30 calendar days after receipt. As stated in the proposed rule and in this preamble above, the generalized list of reasons for which extensions have and have not been granted that is to be posted and updated periodically on *ClinicalTrials.gov* will *not* include any information that might allow a user to identify a specific applicable clinical trial. The intent is to provide responsible parties and members of the public with insight into the types of reasons that have and have not been considered to constitute good cause for an extension. We believe that this approach provides sufficient information about the process for requesting extensions for good cause.

Final Rule

Final § 11.44(e) largely retains the proposal outlined in the NPRM with the following exceptions. First, the final rule replaces the 15 calendar day deadlines (*e.g.,* for submission of results information or an appeal after a request is denied) as proposed in the proposed rule with 30 calendar days in the final rule in response to public comments. Second, the final rule clarifies that some applicable clinical trials may be subject to section 402(j)(3)(E)(vi) of the Public Health Service Act. Third, the final rule adds § 11.44(e) to the list of provisions in § 11.44(e)(1)(i) and § 11.44(e)(2)(ii) regarding the submission deadlines that would otherwise apply. Fourth, formatting changes are made for consistency and clarity. Final § 11.44(e)(1) stipulates that extension requests must be submitted to the Agency via direct electronic submission to *ClinicalTrials.gov* prior to the date on which results information would otherwise be due in accordance with the results information submission deadlines, including one for a previously-granted extension request. Responsible parties are required to submit a description of the reasons that they believe constitute good cause to justify an extension and an estimated extended results information submission date with sufficient detail to allow for evaluation of both requested components.

Under § 11.44(e)(2), a response to the extension request will be communicated electronically via *ClinicalTrials.gov* to the responsible party, providing notice as to whether or not the requested extension has been granted. If a request is granted because it demonstrates good cause, a revised deadline for results information submission will be communicated in the notice. If a request is denied, the deadline for submitting results is the later of the deadline (*e.g.,* 1 year after the primary completion date or the delayed submission deadline if a certification has been filed under subparts (b) or (c)) or 30 calendar days after the date the electronic notice of the denial of the request is sent to the responsible party.

Section 11.44(e)(3) specifies that a responsible party who appeals a denied extension request must submit the appeal to the Director in the format specified at *https://prsinfo.clinicaltrials.gov/* (or successor site) not later than 30 calendar days after the date on which electronic notification of the granting or denial of the request was sent to the responsible party. The appeal must explain why, in the view of the responsible party, the initial decision to deny an extension request or to grant an extension request with a shorter deadline than requested by the responsible party should be overturned or revised (*e.g.,* by providing further elaboration of the grounds for the request or by highlighting factors that justify an extension). Generally, new information should not be submitted upon appeal. The submitted appeal will be considered by the Director or his delegate. If an appeal is granted, a revised deadline for results information submission will be set by the Director and provided to the responsible party in an electronic notification. If the appeal is denied, the deadline for submitting results information will be the later of the original submission deadline or 30 calendar days after the electronic notification of the denial of the appeal is sent to the responsible party. If the appeal of an extension request that was granted with a shorter deadline than was originally requested is denied, the deadline for submitting results information is the later of the deadline specified in the notification granting the extension request or 30 calendar days after the electronic notification of the denial of the appeal is sent to the responsible party.

We note that if the estimated primary completion date is earlier than the actual (or current estimated) primary completion date, a responsible party must update the estimated primary completion date in the clinical trial record to reflect the actual (or revised estimated) primary completion date within 30 calendar days, as required by § 11.64(a)(1)(ii)(I), but should *not* request an extension based on the outdated primary completion date. The fact that the responsible party has updated the primary completion date will be reflected in *ClinicalTrials.gov*, consistent with the handling of all updates under § 11.64.

Posted records of trials that have been granted certification for delayed submission or extension will indicate that results information submission has been delayed by displaying minimal information. This will provide significant information for users to know whether a trial has met the requirements for results information

submission under the final rule. As soon as practicable, we will post on the *ClinicalTrials.gov* Web site, and periodically update, a list of reasons for which extensions have and have not been granted to provide responsible parties and the public with insight into the types of reasons that have and have not been considered to constitute good cause for an extension. We note that entries on this list will not contain any information that might allow a user to identify a specific applicable clinical trial.

§ 11.44(f)—Pediatric Postmarket Surveillance of a Device That Is Not a Clinical Trial

Overview of Proposal

We proposed in § 11.44(f) that results information for a pediatric postmarket surveillance of a device that is not a clinical trial be submitted not later than 30 calendar days after the date that the final report is submitted to FDA. We believe that 30 calendar days provide sufficient time to allow the responsible party to format and submit the information as required by this part.

We noted in the NPRM that we recognize that the proposed deadlines for submitting clinical trial results information under proposed § 11.44(a)–(d) are not well adapted to a pediatric postmarket surveillance of a device that is not a clinical trial. Such surveillances generally do not have a completion date that can be easily measured by the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. However, these surveillances will have a date on which a final report must be sent to the FDA, as specified in the approved postmarket surveillance plan (79 FR 69638).

Comments and Response

One commenter addressed proposed § 11.44(f) and suggested that the timeline submission requirement should apply as to § 11.44(a)–(d). We note that any pediatric postmarket surveillance of a device that is also a clinical trial would be subject to the results information submission deadlines that apply to clinical trials (*e.g.,* standard submission deadline in proposed § 11.44(a)). For a pediatric postmarket surveillance of a device that is not a clinical trial the proposed deadlines § 11.44(a)–(d) are not well adapted. Therefore, the final rule retains the deadline specified in proposed § 11.44(f).

Final Rule

Aside from clarifying that ''device'' means ''device product'' and that some surveillances that are not clinical trials may be subject to section 402(j)(C)(3) of the PHS Act, no changes were made in § 11.44(f) of the final rule, which requires the submission of results information not later than 30 calendar days after the date on which the final report of the approved pediatric postmarket surveillance of a device product as specified in 21 CFR 822.38 is submitted to FDA (*i.e.,* the primary completion date as defined in § 11.10(a)).

4. § 11.48—What constitutes clinical trial results information?

Overview of Proposal

Section 11.48(a) of the NPRM proposed the general requirements for clinical trial results information that would apply to an applicable clinical trial other than a pediatric postmarket surveillance of a device that is not a clinical trial. Proposed § 11.48(b) described the requirements for a pediatric postmarket surveillance of a device that is not a clinical trial. In specifying the results information that must be submitted for a clinical trial, proposed § 11.48(a) separated the data elements into the following general categories of information: (1) Participant flow, (2) demographic and baseline characteristics, (3) outcomes and statistical analyses, (4) adverse event information, (5) administrative information, and (6) additional results information for applicable device clinical trials of unapproved or uncleared devices. The proposal also indicated that whenever possible *ClinicalTrials.gov* will use information submitted during registration to pre-populate the column and row names of the tables of information that are required as part of results submission. We noted that doing so reduces the data entry burden on responsible parties and minimizes the possibility of clerical errors. However, in all cases, the responsible party is required to revise the information, as needed, so that the results information appropriately and accurately reflects the way that data were collected and analyzed in the clinical trial. Each of the categories of results information that are required to be submitted are addressed, in order, below (79 FR 69638).

Comments and Response

Numerous commenters addressed the requirements for clinical trial results information that would apply to an applicable clinical trial. The specific comments are described in the sections of § 11.48 to which they apply. We received one general comment in support of the proposed requirements for results information. We also received one general comment requesting that the Agency minimize the number of fields and amount of data required for clinical trial results information in order to provide responsible parties with more flexibility in reporting the results of different types of trials. Based on more than 7 years of experience operating the results database, we recognize the need for flexibility and generally agree with the commenter. The final rule represents our attempt to balance the statutory requirements with the minimum information needed to understand study results in a way that is consistent across clinical trials and with existing reporting standards, such as the CONSORT statement [Ref. 93] which are used to guide the publication of trial results in peer-reviewed literature.

§ 11.48(a)(1)—Participant Flow

Overview of Proposal

Proposed § 11.48(a)(1) addressed the statutory requirement for the submission of specified participant flow information as part of clinical trial results information. Section 402(j)(3)(C)(i) of the PHS Act specifies that a responsible party must submit ''[a] table of . . . data collected overall and for each arm of the clinical trial to describe the patients who participated in the clinical trial, including the number of patients who dropped out of the clinical trial and the number of patients excluded from the analysis, if any.'' Consistent with this section of the PHS Act and pursuant to our authority under section 402(j)(3)(D)(iii)(IV) of the PHS Act, we proposed in § 11.48(a)(1) to require the submission of the following participant flow information: (1) Participant Flow Arm Information, (2) Pre-assignment Information, and (3) Participant Data. This information permits the construction of a table that shows the number of participants starting the clinical trial and the flow through completion of the trial. In our proposed approach, information about the number of participants excluded from the analysis would not be contained in the participant flow but would be submitted as part of the information about outcome measures specified and described in proposed § 11.48(a)(3). We also described how we intend to continue to provide responsible parties with a means of providing, on an optional basis, additional details about the participant flow in a manner consistent with CONSORT guidelines [Ref. 93] (79 FR 69639). We invited public comments on

the value of providing additional information describing study periods (*e.g.,* wash-out, consecutive cycles of the intervention), particular milestones, and reasons for non-completion on *ClinicalTrials.gov* as well as comments on approaches for collecting this information.

Comments and Response

Commenters addressed specific aspects of the proposed requirements for participant flow information in § 11.48(a)(1). One commenter suggested requiring the submission of information on the number of participants that are enrolled and who complete the trial at the time that the trial ends (instead of at the time of clinical trial results submission). We agree with the commenter that the actual number of participants enrolled in the trial must be provided in a timely manner as specified in §§ 11.28 and 11.64. However, the number of participants completing the trial is considered clinical trial results information that must be submitted in accordance with section 402(j)(3)(C)(i) of the PHS Act and § 11.24. Another commenter suggested requiring the submission of information on the number of participants not completing the trial by sex and gender and in a standardized format, citing associated scientific principles. While we agree with the commenter on the potential value of such information, requirements regarding which data must be collected during a clinical trial are outside the scope of this rule. We therefore are not proposing to make submitting the requested participant flow information a requirement, but we do intend to evaluate ways to accommodate the submission of any such available information. We did not receive any comments on the value of providing additional information for describing study periods, milestones, and reasons for non-completion on *ClinicalTrials.gov* or on approaches for collecting this information. However, one commenter provided general support for providing Pre-assignment Information.

Final Rule

Taking into consideration the comments, as well as the statutory requirements for clinical trial results information, we are generally maintaining the approach for participant flow information described in the NPRM. However, we are providing clarification on certain aspects of the requirements, based on our operational experience and routine queries received from users. First, we provide additional elaboration to clarify the information that is required to be provided as part of the brief description of each arm. Second, we clarify the definition of Pre-assignment Information in § 11.48(a)(1)(ii). The proposed definition indicated that Pre-assignment Information consists of ''[a] description of significant events affecting the number of human subjects enrolled in the clinical trial but not assigned to an arm, if any.'' The phrase ''affecting the number of'' may incorrectly imply that the actual number of human subjects enrolled changes based on a pre-assignment event. Instead, the intent is to describe events that occur between enrollment and assignment to an arm that are planned as part of the study design and other events that lead to differences in the number of human subjects enrolled and the number of human subjects assigned to an arm. Third, we explain the terms ''started'' and ''completed,'' which are used to describe Participant Data in § 11.48(a)(1)(iii). Fourth, we address requirements for clinical trials that assign participants to arms based on units other than participants (*e.g.,* lesions, eyes, implants). While the NPRM included a proposal for how such information is specified when reporting an outcome measure in § 11.48(a)(3)(ii), Analysis Population Information, it did not address similar information in § 11.48(a)(1), Participant flow and § 11.48(a)(2) Demographic and baseline characteristics.

Final § 11.48(a)(1) requires the submission of the following participant flow information: (1) Participant Flow Arm Information, consisting of ''[a] brief description of each arm used for describing the flow of human subjects through the clinical trial, including a descriptive title used to identify each arm''; (2) Pre-assignment Information, consisting of ''[a] description of significant events in the clinical trial that occur after enrollment and prior to assignment of human subjects to an arm, if any''; and (3) Participant Data, which is ''[t]he number of human subjects that started and completed the clinical trial, by arm. If assignment is based on a unit other than participants, also include a description of the unit of assignment and the number of units that started and completed the clinical trial, by arm.'' This information permits the construction of a table that shows the flow of participants through the clinical trial, with each participant represented in only one arm. Information about the number of participants excluded from the analysis is not contained in the participant flow; it is submitted as part of the information about outcome measures (§ 11.48(a)(3), Outcomes and statistical analyses). *ClinicalTrials.gov* will use the Arm Information, Intervention Name, and Intervention Description data elements (submitted as part of clinical trial registration information) to provide the responsible party with an option for pre-populating table column names and descriptions for Participant Flow Arm Information. The responsible party will review and edit the information as needed to ensure that it appropriately and accurately reflects the participant flow for the clinical trial, or the responsible party may instead define new arms to reflect how participants were assigned to arms. In general, the Participant Flow Arm Information must include all arms to which participants were assignedand must contain sufficient details to understand the arms to which participants were assigned and the intervention strategy used in each arm. The amount and level of detail are similar to what is described in § 11.10(b) for the arm and intervention data elements that are used to pre-populate Participant Flow Arm Information.

Pre-assignment Information is collected in a free text field to allow the responsible party to explain significant events that occur between the enrollment of human subjects and their assignment to an arm. These events may be planned as part of the study design or unplanned. An example of a significant event that is planned as part of the study design is a run-in period during which all participants receive an intervention, which may result in identifying participants who are not eligible to continue in the study or may otherwise influence assignment to an arm. An example of an unplanned event is the voluntary withdrawal of a participant prior to assignment to an arm. Either event may result in the number of human subjects starting the trial (*e.g.,* assigned to an arm) being fewer than the total number of human subjects enrolled. Pre-assignment Information is where the responsible party describes any such differences. As part of Participant Data, the responsible party provides the number of human subjects that started and completed each arm. The number of participants that ''started'' the clinical trial means the number of participants assigned to the arm (regardless of whether these participants received the assigned intervention). The meaning of the number of participants that ''completed'' the arm may vary, based on the specific context of the clinical trial. However, if there is more than one

period (*e.g.,* a discrete stage) in the clinical trial, the meaning of the number of participants starting and completing is in the context of initial assignment and the specific period. Specifically, ''started'' in the first period (and the overall clinical trial) means the number of participants assigned to each arm, and ''started'' in subsequent periods (if any) means the number of participants initiating each period of the clinical trial in each arm. In order to retain the flexibility desired by responsible parties in reporting results, we do not intend to define this further. However, we will implement an optional data element to allow responsible parties to explain the meaning of ''started'' and/or ''completed'' in the context of their specific clinical trial. If the assignment of participants to an arm is based on a unit other than human subjects (*e.g.,* lesions, eyes, implants), the responsible party must also provide, in addition to participants, the type and number of units that started and completed the clinical trial, by arm. Based on our experience with submitted results information and routine queries from users of *ClinicalTrials.gov*, this information is necessary for accurately representing the assignment strategy and for interpreting similar information on the units analyzed in Analysis Population Information for Demographic and baseline characteristics in § 11.48(a)(2)(ii) and Outcomes and statistical analyses in § 11.48(a)(3)(ii). Therefore, consistent with section 402(j)(3)(C)(i) of the PHS Act and pursuant to our authority under section 402(j)(3)(D)(iii)(IV) of the PHS Act, final § 11.48(a)(1) requires the submission of the following participant flow information: (1) Participant Flow Arm Information, (2) Pre-assignment Information, and (3) Participant Data.

Although we did not receive any comments in response to our request for comment on the topic of describing study periods, milestones, and reasons for non-completion on *ClinicalTrials.gov*, we intend to continue to provide responsible parties with a means of submitting, on an optional basis, additional details about the participant flow in a manner consistent with CONSORT guidelines [Ref. 93]. This information consists of details about the flow of participants through different periods or milestones defined for the clinical trial and the reason(s) why participants did not complete the clinical trial or reach a particular milestone. Clinical trials often proceed through multiple periods (*e.g.,* wash-out, consecutive cycles of the intervention), and having information about the participant flow in each period and the reasons why participants did not complete the clinical trial or reach a particular milestone, if applicable, improves users' understanding of the clinical trial results data. Clinical trials vary considerably in their design, and some may not include specific periods or milestones. However, when a study does include such aspects, we will continue to encourage responsible parties to provide clinical trial results information in a manner that most clearly describes the study design and what happened to participants as they progressed through the study. We intend to provide additional guidance, including case examples, to help responsible parties understand how to optimally present various study designs.

§ 11.48(a)(2)—Demographic and Baseline Characteristics

Overview of Proposal

Proposed § 11.48(a)(2) addressed the statutory requirement for the submission of demographic and baseline characteristics as part of clinical trial results information. Section 402(j)(3)(C)(i) of the PHS Act specifies that a responsible party must submit ''[a] table of the demographic and baseline data collected overall and for each arm of the clinical trial to describe the patients who participated in the clinical trial . . .'' (79 FR 69639). Consistent with this section of the PHS Act, the Agency proposed in § 11.48(a)(2) to require ''[i]nformation for completing a table of demographic and baseline measures and data collected by arm or comparison group and for the entire population of human subjects who participated in the clinical trial.'' The information must include the following: (i) Baseline Characteristics Arm/Group Information; (ii) Overall Number of Baseline Participants; (iii) Baseline Measure Information, to include the Name and Description of the measure, Measure Type, Measure of Dispersion, and Unit of measure; and (iv) Baseline Measure Data. We further proposed that Baseline Measure Information must include ''[a] description of each baseline or demographic characteristic measured in the clinical trial, including age, gender, and any other measure(s) that were assessed at baseline and used in the analysis of outcome measures in accordance with § 11.48(a)(3).'' We invited public comment on the sufficiency of this proposed approach for submitting baseline characteristics as well as whether we should require the submission of additional demographic or baseline characteristics collected during the clinical trial that are common across many trials, such as country-of-origin or country-of-residence. We also invited comment on whether the list of proposed choices for measures of central tendency and of dispersion was adequate to provide an accurate description of the measures used in any clinical trial (79 FR 69640).

Comments and Response

Commenters addressed specific aspects of the proposed requirements for demographic and baseline characteristics in § 11.48(a)(2). One commenter provided general support for the proposed baseline characteristics requirements. Some commenters supported adding a requirement for reporting race and ethnicity information, with several commenters citing similar FDA and NIH requirements. One commenter stated that having race and ethnicity information was important for different groups ''seeking to understand how representative minority populations are in [applicable clinical trials] . . .'' Some of these commenters also recommended including an option to specify that race and ethnicity information was not collected. While we did not propose to require race and ethnicity information because of a concerns that this information may not be routinely collected during all clinical trials, we agree that providing the responsible party with a mechanism to indicate that race and/or ethnicity information was not collected would address this concern. Therefore, the final rule adds a requirement for the reporting of race and ethnicity information, or an indication that such information was not collected during the trial, as a component of Baseline Measure Information. The final rule follows the same approach to indicating that information was not collected during the trial as for other baseline measures required by *ClinicalTrials.gov* (*e.g.,* age, sex/gender). One commenter indicated that country of origin information ''could be an important data point'' to require but did not provide further elaboration on why it is important. Although it may be important for some clinical trials, in considering other commenters concerns about additional requirements (noted below) as well as the addition of a requirement to submit race and ethnicity informatoin, we are not persuaded that the benefits of requiring country-of-origin information would outweigh the burdens. However, we will, continue to make available ''region of enrollment'' as part of the limited list of options for Baseline

Measure Information to facilitate the optional reporting of such information if it was assessed at baseline. One commenter recommended that the term ''gender'' be replaced by ''sex.'' We partially addressed this issue in § 11.10, and to address the same issue in the context of clinical trial results information, we are revising the term ''gender'' to ''sex/gender'' to indicate that the submission of Baseline Measure Information on sex and/or gender would meet the requirement. Other commenters opposed any additional requirements for demographic information, citing concerns that expanded reporting requirements would lead to future requirements to collect such data during a trial. As explained in proposed § 11.48(a)(2)(iii), only summary data for measures assessed at baseline are required to be reported, and the final rule does not impose requirements on the design or conduct of clinical trials or on the data that must be collected during clinical trials.

After consideration of the comments, we believe it is appropriate in the final rule to limit the requirement to report any measure(s) assessed at baseline and used in the analysis of outcome measure(s) in § 11.48(a)(2)(iii) to those baseline measure(s) used in the analysis of primary outcome measure(s). One commenter suggested that baseline measures related to outcome measures be reported as part of outcome measure information in proposed § 11.48(a)(3). We acknowledge that, in limited circumstances, the arms or groups used for demographics and baseline characteristics may differ from those used in the primary outcome measure and agree with the commenter that providing such Baseline Measure Information as part of Outcome Measure Information would be appropriate in such circumstances. When relevant, the final rule also permits the reporting of baseline measure information as a component of both demographic and baseline characteristics in § 11.48(a)(2) as well as outcomes and statistical analyses in § 11.48(a)(3). In addition, we will continue to evaluate methods for displaying results information on ClinicalTrials.gov to improve linking these two relevant sections when the baseline and outcome measures are related.

Based on our experience with submitted results information and routine queries from users, we note that some clinical trials include baseline measures and outcome measures that are based on units of analysis other than participants. While the NPRM did not address how such information could be specified in proposed § 11.48(a)(2), Demographic and baseline characteristics, it did include a proposal for reporting such information as an outcome measure in § 11.48(a)(3)(ii) Analysis Population Information. To address this inadvertent omission and facilitate the accurate submission of Baseline Measure Information and Baseline Measure Data in a manner that is consistent with the design, conduct and analysis of the clinical trial, the final rule adds similar data elements to § 11.48(a)(2) for the limited cases in which units of analysis are other than participants (*e.g.,* lesions, eyes, implants). We also note that if such a requirement were not added, it would not be possible for a responsible party to submit baseline measure(s) that were assessed at baseline and used in the analysis of the primary outcome measures(s), when the unit of analysis for the primary outcome measure(s) is other than participants. We also add an element to describe the analysis population when the Overall Number of Baseline Participants (or units) differs from the number of human subjects (or units) assigned to an arm or comparison group, similar to Analysis Population Description in § 11.48(a)(3)(ii)(C). Analysis Population Description was added to Demographic and baseline characteristics as an optional data element in January 2013 in response to queries routinely received from responsible parties as well as our experience with submitted results information. Based on a review of clinical trials with results posted on *ClinicalTrials.gov,* the number of participants analyzed in Demographic and baseline characteristics differed from the number assigned to an arm in 15 percent of clinical trials. The addition of this data element is therefore necessary to enable users of *ClinicalTrials.gov* to understand why some participants (or units) were excluded from the analysis of Demographic and baseline characteristics. These data elements in final § 11.48(a)(2) are consistent with section 402(j)(3)(C)(i) of the PHS Act and are promulgated pursuant to our authority under section 402(j)(3)(D)(iii)(IV) of the PHS Act.

We invited comments on whether the lists of proposed choices for Measure Type and Measure of Dispersion were adequate, but we did not receive any specific comments on this topic. However, based on our experience with submitted results information and routine queries from users of *ClinicalTrial.gov,* we have identified two issues with the following limited list of options for Measure Type proposed in the NPRM preamble: ''Number,'' ''mean,'' ''median,'' ''least squares mean,'' ''geometric mean,'' and ''log mean.'' First, because the ''log mean'' option is not needed, we have excluded it from the limited list of options for Measure Type. Of the more than 22,000 records with posted results on *ClinicalTrials.gov* as of July 2016, only 3 indicated ''log mean'' in Baseline Measure Information, and in each case the data were the mean of log transformed data (rather than a logarithmic mean) and should have been specified as a Measure Type of ''mean'' instead. Second, as discussed in this preamble for Outcome measures and statistical analyses, we also add ''geometric least squares mean'' to the list of options for Measure Type. Third, the ''number'' option is not sufficiently granular to allow for discrimination among different methods of aggregation that use ''number'' for Measure Type (such as count of participants or percentage of participants). To address this, we are adding two additional options to Measure Type to specify whether the number is a ''count of participants'' or a ''count of units.'' These choices will improve the clarity of results data by making such counts unambiguous, thereby ensuring that these data are properly interpreted by human users as well as (semi-) automated systems.

Final Rule

Taking into consideration the comments, our experience with the *ClinicalTrials.gov* data bank, and the statutory requirements for clinical trial results information, we are modifying the NPRM approach for Baseline Measure Information to specify that Demographic and baseline characteristics includes a new requirement to provide race and ethnicity information, if collected, or indicate that it was not collected, and modifies the requirement to provide other measures assessed at baseline to those used in the analysis of a primary outcome measure. In addition, based on our operational experience and routine queries from users, we add provisions in final § 11.48(a)(2)(ii), Baseline Analysis Population Information to address how the responsible party provides demographic and baseline characteristics when the unit of analysis is not human subjects and how to describe the analysis population, if needed. Final § 11.48(a)(2)(v) also explains how to specify the number of baseline participants (and units) analyzed, if different from the Overall Number of Baseline Participants or Units Analyzed. Additional elaboration

is provided on the information required to be submitted as a brief description of each arm/group (a similar omission was described for § 11.48(a)(1)), the use of ''categories'' used to submit Baseline Measure Data, and options for specifying Measure Type. We have made minor revisions to clarify the Name and description of the measure in final § 11.48(a)(2)(iii)(A) to indicate that the information must include ''any categories that are used to submit Baseline Measure Data'' (revised from the proposed broader phrasing of ''any categories that are used in submitting results''). We also have revised the description of the population for whom Baseline Measure Data is provided in § 11.48(a)(2)(iv) (proposed ''human subjects who participated in the clinical trial'') to be consistent with a similar description for Overall Number of Baseline Participants in § 11.48(a)(2)(ii)(A) (''human subjects for whom baseline characteristics were measured''). Final § 11.48(a)(2) requires the submission of the following demographic and baseline characteristic information: (i) Baseline Characteristics Arm/Group Information; (ii) Baseline Analysis Population Information; (iii) Baseline Measure Information; (iv) Baseline Measure Data; and (v) Number of baseline participants (and units), if different from Overall Number of Baseline Participants or Units Analyzed.

ClinicalTrials.gov will use the Arm Information, Intervention Name, and Intervention Description data elements (submitted as clinical trial registration information) as well as Participant Flow Arm Information to provide the responsible party with options for pre-populating table column names and descriptions for Baseline Characteristics Arm/Group Information (described in final § 11.48(a)(2)(i)). The responsible party will review and edit the information as needed to ensure that it appropriately and accurately reflects the baseline arms/groups for the clinical trial, or the responsible party may instead define new groups to reflect how baseline information was analyzed. As described in the discussion of the term ''comparison group'' in § 11.10(a) of the preamble, the reference to comparison groups recognizes that when data collected during clinical trials are analyzed, the data are often aggregated into groupings of human subjects (*i.e.,* comparison groups) other than the arms to which the subjects were assigned for the study. It is expected that Baseline Characteristics Arm/Group Information will be the same as Participant Flow Arm Information, unless human subjects were analyzed in groups that are different from those to which they were assigned. In this situation, there must be sufficient detail to understand how the arm(s) or comparison groups used for submitting Baseline Characteristics Arm/Group Information were derived from Participant Flow Arm Information. In general, Baseline Characteristics Arm/Group Information must include all participants assessed at baseline, with each participant belonging to only one arm or comparison group, as specified in the pre-specified protocol and/or SAP. Baseline Characteristics Arm/Group Information must also include sufficient detail to understand the intervention strategy being described in that arm/group, similar to what is described in this preamble for Participant Flow Arm Information in § 11.48(a)(1).

Baseline Analysis Population Information, as described in final § 11.48(a)(2)(ii), consists of (A) Overall Number of Baseline Participants, (B) Overall Number of Units Analyzed, and (C) Analysis Population Description. Baseline Analysis Population Information is similar to that described for Analysis Population Information for outcome measures in § 11.48(a)(3)(ii). The Overall Number of Baseline Participants is defined as the ''[t]he total number of human subjects for whom baseline characteristics were measured, by arm or comparison group, and overall.'' Overall Number of Baseline Participants is necessary to indicate whether some subjects enrolled in the clinical trial were not measured at baseline (*e.g.,* because they dropped out of the clinical trial before that point in time) and to help ensure that results information is submitted for all subjects who were measured at baseline. If any of the demographic or baseline characteristics are based on a unit other than human subjects (*e.g.,* lesions, eyes, implants), the responsible party is also required to provide the Overall Number of Units Analyzed, which is defined as ''. . . a description of the unit of analysis and the number of units for which baseline measures were measured and analyzed, by arm or comparison group and overall.'' In addition, the Analysis Population Description in baseline must be used ''[i]f the Overall Number of Baseline Participants (or units) differs from the number of human subjects (or units) assigned to the arm or comparison group and overall, [with] a brief description of the reason(s) for the difference.''

Baseline Measure Information, as described in § 11.48(a)(2)(iii), consists of ''[a] description of each baseline or demographic characteristic measured in the clinical trial, including age, sex/gender, race, ethnicity (if collected under the protocol), and any other measure(s) that were assessed at baseline and are used in the analysis of the primary outcome measure(s) in accordance with § 11.48(a)(3).'' If any Baseline Measure Information (described in § 11.48(a)(2)(iii)) is not measured in the clinical trial (*e.g.,* age, sex/gender, race and ethnicity), *ClinicalTrials.gov* will provide a mechanism for the responsible party to indicate that such information was not collected. A responsible party must submit demographic and baseline characteristics using the following limited list of options for Baseline Measure Information: ''Age,'' ''sex/gender,'' ''race and ethnicity,'' ''region of enrollment'' (if assessed at baseline), and ''study-specific measure(s),'' by arm or comparison group and overall for the clinical trial. Age information must be submitted as ''age, continuous'' (*e.g.,* for Measure Types of ''mean'' or ''median''), ''age, categorical'' (pre-defined categories of <18 years, 18 to 65 years, and >65 years), or ''age, customized'' (age categories defined by responsible party). For sex/gender data, the responsible party must submit using ''sex, male, female'' (pre-formatted categories of male and female) and/or ''gender, customized'' (gender categories defined by the responsible party). The responsible party may use the description of the measure to provide additional, free-text information about the collection and/or reporting methods used for sex and/or gender information. Race and ethnicity data must be submitted as ''race (NIH/OMB),'' ''ethnicity (NIH/OMB),'' or ''race/ethnicity, customized.'' The options that reference NIH/OMB reflect the classification system of the Office of Management and Budget (OMB) (see 62 FR 58782, Oct. 30, 1997), which has been adopted by Federal agencies, including NIH. Alternatively, the responsible party may select ''race/ethnicity, customized'' in order to customize race and ethnicity categories for consistency with how information was collected in the protocol for the clinical trial, if different from the NIH/OMB classification. If region of enrollment information is provided, the measure information will be pre-filled with the countries described for Facility Information in § 11.28(a)(2)(iii)(C), but this information can be edited as needed. Responsible parties must select from this limited list of options for Baseline Measure Information to ensure that the required information is

provided and to allow for the identification of such information in a search by users of the public site. In addition, *ClinicalTrials.gov* accommodates the submission of information to describe an unlimited number of customized demographic and baseline characteristics (using the ''study-specific measure'' option). In general, we cannot specify in advance which other demographic and baseline characteristics would be provided for a particular clinical trial. Only those conducting the clinical trial will know which characteristics are important for their clinical trial and which were actually collected. Important demographic and baseline characteristics are those that a responsible party determines are useful for comparing participants across comparison groups and for describing the population enrolled in the clinical trial. Although we cannot specify these characteristics in advance, we do believe it is important that baseline measures include any characteristic used in assessing primary outcome measure(s). For example, if an outcome measure compares a subject's blood pressure after 6 weeks of receiving a particular intervention, the baseline measure of blood pressure must be submitted. Similarly, if a clinical trial includes a statistical analysis of a primary outcome measure that uses baseline data from participants enrolled in the clinical trial as part of the calculation (*e.g.,* a regression analysis), it is necessary to submit the relevant baseline data. The use of these baseline data in analyzing the primary outcome measure indicates that these data would have been collected during the clinical trial and would be important to the interpretation of results. In the limited circumstance in which Baseline Characteristics Arm/Group Information is different from the Arms/Groups used in the analysis of the primary outcome measure(s), it is acceptable to provide the relevant Baseline Measure Information only as part of Outcome Measure Information.

For each measure, Baseline Measure Information in § 11.48(a)(2)(iii) must include the following elements: ''(A) Name and description of the measure, including any categories that are used to submit Baseline Measure Data; (B) Measure Type and Measure of Dispersion [for] each baseline measure submitted, an indication of the type of data to be submitted and the associated measure of dispersion; [and] (C) Unit of Measure.'' Providing Baseline Measure Information in this structured manner is intended to ensure that the information is meaningful to users, ensure that submitted information is complete, and improve the comparability of information across clinical trials. With respect to the categories that are used to submit Baseline Measure Data, in our experience operating *ClinicalTrials.gov,* we have observed that responsible parties use categories for two general types of information: Either a list of mutually exclusive and exhaustive categories to which each participant belongs to one and only one (*e.g.,* participants with history of smoking, no history of smoking, unknown) or a list of items that are not mutually exclusive and exhaustive for which a single participant may be represented in more than one row (or not all) (exposure to ''A,'' ''B,'' and/or ''C''). To distinguish these two different types of information and to allow for improved options for validation (*e.g.,* the system can ensure that the sum of participants in mutually exclusive and exhaustive categories is the same as the overall number of baseline participants), responsible parties may indicate which information type is being reported. When specifying the Measure Type, the responsible party is required to select one option from the following limited list of options: ''Count of participants,'' ''count of units,'' ''number,'' ''mean,'' ''median,'' ''least squares mean,'' ''geometric mean,'' and ''geometric least squares mean.'' When specifying the associated Measure of Dispersion, the responsible party is required to select one option from the following limited list of options: ''Standard deviation,'' ''inter-quartile range,'' ''full range,'' and ''not applicable'' (which would be permitted only if the specified measure type is ''count of participants,'' ''count of units,'' or ''number''). No ''other'' option is available for either Measure Type or Measure of Dispersion, but responsible parties have the option of voluntarily providing additional information about the baseline measures as part of a free-text description of the baseline measure. Unit of Measure describes what is being quantified by the data (*e.g.,* blood pressure in ''millimeters of mercury'' or ''participants''). Each baseline measure can have only one Unit of Measure.

Final § 11.48(a)(2)(iv) specifies that Baseline Measure Data consists of ''[t]he value(s) for each submitted baseline measure, by arm or comparison group and for the entire population of human subjects . . .'' Section 11.48(a)(2)(v) indicates that, for each submitted baseline measure, the number of baseline participants (and units) must be specified if different from the Overall Number of Baseline Participants or Overall Number of Units Analyzed (*e.g.,* a participant was unable to complete one of the baseline assessments). The ''[n]umber of baseline participants (and units)'' is provided ''by arm or comparison group and overall'' as part of Baseline Measure Data.

§ 11.48(a)(3)—Outcomes and Statistical Analyses

Overview of Proposal

Proposed § 11.48(a)(3) addressed the statutory requirement for the submission of outcomes and statistical analyses as part of clinical trial results information. Section 402(j)(3)(C)(ii) of the PHS Act specifies that a responsible party must submit ''[t]he primary and secondary outcome measures as submitted under paragraph (2)(A)(ii)(I)(ll), and a table of values for each of the primary and secondary outcome measures for each arm of the clinical trial, including the results of scientifically appropriate tests of the statistical significance of such outcome measures'' (79 FR 69640). Consistent with this section of the PHS Act, the Agency proposed in § 11.48(a)(3) to require ''[i]nformation for completing a table of data for each primary and secondary outcome measure by arm or comparison group, including the result(s) of scientifically appropriate statistical analyses that were performed on the outcome measure data, if any.'' The NPRM noted that the information must include the following: (i) Outcome Measure Arm/Group Information; (ii) Analysis Population Information; (iii) Outcome Measure Information, to include the Name of the specific measure, Description of the metric, Time point(s) at which the measurement was assessed, Outcome Measure Type, Outcome Measure Reporting Status, Measure Type, to include type of data and related measure of dispersion or precision, and Unit of measure; (iv) Outcome Measure Data; and (v) Statistical Analyses information for results of scientifically appropriate statistical analyses. The NPRM included options that could be selected to describe the type of data and related measure of dispersion or precision and invited public comment on whether the proposed options were sufficient for collecting data from the full range of clinical trials that would be subject to the proposed rule. Statistical Analyses were proposed to be defined as ''[r]esult(s) of scientifically appropriate statistical analyses, if any . . .'' The criteria for what would be considered scientifically appropriate were proposed in § 11.48(a)(3)(v) as ''including any statistical analysis that is: (A) Pre-

specified in the protocol and/or statistical analysis plan [SAP] that was performed on the outcome measure data, (B) Made public by the sponsor or responsible party prior to the date on which results information is submitted for all primary and secondary outcome measures studied in the clinical trial, or (C) Conducted in response to a request made by the U.S. Food and Drug Administration prior to the date on which complete clinical trial results information is submitted for all of the primary outcome measures studied in the clinical trial.'' We invited public comment on these and other criteria that the Agency should consider when determining what constitutes a scientifically appropriate statistical analysis. Finally, the NPRM described approaches for reporting information for outcome measures and statistical analyses in the following situations: (1) When a trial is terminated before data are collected for one or more of the pre-specified outcome measures and (2) when outcome measure data are collected, but the actual enrollment falls well below the target enrollment. We invited public comments on other way to highlight the limitations of the submitted data when either situation occurs (79 FR 69643).

Comments and Response

Commenters addressed specific aspects of the proposed requirements for Outcomes and statistical analyses in § 11.48(a)(3). Most of the commenters addressed the proposed criteria for determining when a statistical analysis would be considered scientifically appropriate. Many of these commenters expressed concern that the proposal may require statistical analyses for exploratory outcome measures described in the protocol and/or SAP to be reported. Other commenters indicated that some statistical analyses associated with a primary or secondary outcome measure are considered exploratory, post-hoc, or of sub-groups, rather than primary, and they requested clarification on which of these would be required to be reported. We clarify that the proposal was intended to require the submission of statistical analyses for only primary and secondary outcome measures and, therefore, would not have the effect of requiring statistical analyses for other pre-specified or post-hoc outcome measures (including for sub-groups) not considered primary or secondary outcome measures in the protocol and/or SAP. Similarly, we interpret § 11.48(a)(3)(v) to exclude statistical analyses considered exploratory, even if they are pre-specified in the protocol and/or SAP for primary and secondary outcome measures. In addition, the requirement to submit statistical analyses is limited to those that inform the interpretation of the primary and secondary Outcome Measure Information and Outcome Measure Data that are submitted. Alternatively stated, if the statistical analysis does not rely on data that are specified as primary or secondary outcome measure information in § 11.48(a)(3)(i)–(iv), that analysis does not need to be submitted. For example, if a statistical analysis is requested by FDA for a primary outcome measure based on a different analysis population or is limited to certain sub-groups not summarized in the primary or secondary Outcome Measure Information or Outcome Measure Data, that analysis would generally not meet this requirement. To help the public understand when a reported statistical analysis is pre-specified or post-hoc, the responsible party may voluntarily provide additional information in the accompanying free-text fields as needed to support an understanding of the nature of the analysis.

One commenter suggested that the statistical analysis requirements be applied only to the primary outcome measure(s). Section 402(j)(3)(C)(ii) of the PHS Act requires the submission of ''the results of all scientifically appropriate tests of statistical significance of [primary and secondary] outcome measures.'' However, based on our interpretation of which statistical tests are scientifically appropriate, we are limiting some statistical analysis reporting requirements to primary outcome measures, as described below. Other commenters suggested that scientifically appropriate analyses done in response to an FDA request be limited to the primary outcome measure(s), with one noting that not all FDA-requested analyses are determined to be relevant; another commenter expressed concern that reporting statistical analyses without proper context could be confusing to the public, particularly if analyses requested by FDA were not originally specified in the protocol or analysis plan. This commenter also indicated that clinical trial results presented on *ClinicalTrials.gov* should always be based on the CSR submitted to FDA or other health authorities. For the purposes of results information reporting under the final rule, the results of all scientifically appropriate statistical analyses (as defined in § 11.48(a)(3)(v)) for all pre-specified primary and secondary outcome measures must be reported to *ClinicalTrials.gov.* When these analyses are the same as analyses reported to other regulatory authorities in CSRs, it would be reasonable to use the CSR as the source document for reporting. We further clarify that the requirement for reporting statistical analyses made public by the sponsor or responsible party is limited to analyses of primary outcome measure(s) conducted prior to the date on which clinical trial information about that primary outcome measure is submitted to *ClinicalTrials.gov.* We clarify that the requirement for reporting statistical analyses conducted in response to a request by FDA, which is already limited to analyses of the primary outcome measures, is further limited to those analyses of primary outcome measures for which results information has not yet been submitted to *ClinicalTrials.gov.* That is, primary outcome measures are not required to be updated under § 11.64(a) with statistical analyses conducted in response to a request made by FDA, if such analyses are conducted after clinical trial results information is submitted for the primary outcome measure(s) to which the statistical analysis applies.

In addition, as previously stated, the requirement is limited to statistical analyses that rely on the outcome measure data submitted. We also note that *ClinicalTrials.gov* includes optional free-text fields to allow responsible parties the option to provide additional descriptive information about any submitted statistical analysis, including information regarding why the analysis was done, why it is being reported (*e.g.,* in the case of an FDA-requested analysis), and any limitations of the analysis. This descriptive information should generally not include interpretations of results or conclusions about the analyses because of concerns regarding the introduction of bias discussed in greater detail elsewhere in the preamble. One commenter indicated that statistical analyses requested by FDA may contain confidential commercial information and suggested that the results of statistical analyses should be required to be submitted only when pre-specified in the protocol or SAP. As such, the final rule retains the proposed criteria, with the clarification that statistical analyses conducted in response to a request from FDA are limited to those performed on primary outcome measures. We believe that these criteria identify those statistical analyses that either the responsible party or FDA considers scientifically appropriate. We believe that excluding from the requirement analyses that were

prespecified as ''exploratory'' or that were requested by FDA on outcomes other than the primary outcome measure(s) appropriately balances the reporting burden with the informational benefit.

Several commenters suggested that the proposed structure of, and drop-down choices for, the Statistical Analysis Overview, Statistical Test of Hypothesis, and Method of Estimation elements are too rigid for non-drug/device studies and smaller studies. We note that the scope of this rule is limited to studies of drug products (including biological products) and device products. To help ensure that all required statistical analyses can be fully accommodated, we will provide a general ''other'' option that can be used to describe and report the results of statistical analyses that cannot be submitted using the options available for Statistical Test of Hypothesis and Method of Estimation. In addition, the list of options for describing the procedure for Statistical Test of Hypothesis and the estimation parameter for Method of Estimation both include an ''other'' option, and free-text fields are provided for additional explanation, as needed. Commenters suggested that the proposed options for type of statistical test conducted (as part of Statistical Analysis Overview) be expanded from ''superiority,'' ''non-inferiority,'' ''equivalence,'' and ''not applicable'' to include ''estimation'' (*e.g.,* rate of events in a given arm) and ''descriptive'' (*e.g.,* safety analyses). We note that EMA's EudraCT results data bank has a similar data element named ''Analysis type'' and uses the following list of options: ''equivalence,'' ''non-inferiority,'' ''superiority,'' and ''other'' [Ref. 98a]. To accommodate these comments and align with EudraCT more closely, we are modifying the list of options for the type of statistical test conducted by replacing ''not applicable'' with ''other'' and requiring a description of the type of analysis if the ''other'' option is selected. One commenter suggested that, based on deficiencies in reporting found in their analysis [Ref. 14], the final rule should require the specification of the non-inferiority or equivalence margin. We note that although this recommendation is consistent with the proposal in section IV.C.4 of the NPRM, the proposed codified provision inadvertently omitted mention of the equivalence analysis. This has been corrected in the final rule. One commenter provided general support for the proposed requirement for Analysis Population Description as part of Analysis Population Information.

We invited comments on whether the list of proposed choices for Measure Type and Measure of Dispersion or Precision was adequate. One commenter requested that ''geometric least squares mean'' be added to the list of choices. We know from a similar request from a *ClinicalTrials.gov* user that this measure is useful when summarizing data evaluating pharmacokinetics. Based on this comment and our experience, we are adding ''geometric least squares mean'' to the list of choices for Measure Type in both Demographic and baseline characteristics and Outcomes and statistical analyses. In addition, based on operational experience and routine queries from users, we have identified two other issues with the proposed list of options for Measure Type (*i.e.,* ''number,'' ''mean,'' ''median,'' ''least squares mean,'' ''geometric mean,'' and ''log mean.'' As described in the Comments and Response section for § 11.48(a)(2), we have excluded the ''log mean'' option from the list of options in the final rule because it is not needed. Second, as also described in this preamble for § 11.48(a)(2), the ''number'' option is not sufficiently granular to allow for discrimination among different methods of aggregation that use ''number'' as the Measure Type (such as count of participants or percentage of participants). To address this, we are adding two options to Measure Type to allow responsible parties to specify whether the number is a ''count of participants'' or a ''count of units''. We note that this modification more closely aligns the data fields with the EMA's EudraCT results data bank [Ref. 98a], which distinguishes between ''countable'' and ''measurable'' types of data. The final rule also updates ''Measure Type'' to ''Measure Type and Measure of Dispersion or Precision'' for consistency with the similar data element ''Measure Type and Measure of Dispersion'' in § 11.48(a)(2)(iii)(B).

We also requested comments on the proposed approach for reporting outcome measure information when (1) a trial is terminated before data are collected for one or more of the pre-specified outcome measures and (2) when outcome measure data are collected but the actual enrollment falls well below the target enrollment. For the first situation, we proposed that the responsible party may specify zero (''0'') for the Number of Participants Analyzed and that Outcome Measure Data would not need to be submitted. The responsible party would still be expected to provide the clinical trial results information in proposed § 11.48(a)(1),(2), and (4) (79 FR 69642). For the second situation, we proposed that collected results information for the primary or secondary outcome measure must be submitted but statistical analysis information would not be expected to be submitted because it would not be considered scientifically valid (79 FR 69643). We received comments supporting full reporting of results information for terminated or withdrawn studies. A study with an Overall Recruitment Status of ''withdrawn'' does not include any enrolled participants and would not require results information submission. We received one comment on the second situation, in which outcome measure data are required to be submitted for a clinical trial in which actual enrollment falls well below the target enrollment. The commenter was concerned about the misinterpretation of such results and suggested that the final rule require the responsible party to provide additional information about the limitations of the data. We note that, in this particular situation, the posted study record would clearly reflect that the trial was terminated (*i.e.,* the responsible party submitted the Overall Recruitment Status as ''terminated''), and we intend to include information on the posted study record so that the public can easily see when actual enrollment was below the target enrollment goals (using information from the Enrollment data element and submitted estimated and actual values). We believe that this information will make it easier for the public to consistently identify across studies the specific limitations raised by the commenter, thereby reducing the need to make this a requirement. However, we agree that providing additional information about the limitations of the clinical trial and/or the collected data may be helpful in this and other situations, and we strongly encourage responsible parties to use the related free-text fields and/or the optional Limitations and Caveats data element to provide such information, when appropriate. Additional relevant comments were received in the context of waivers and are addressed in § 11.54, accordingly.

Final Rule

Taking into consideration the comments, our experience operating the *ClinicalTrials.gov* data bank, and the statutory requirements for clinical trial results information, the final rule modifies the proposed approach for Outcome measures and statistical analyses. We clarify in § 11.48(a)(3)(v) that one type of scientifically

appropriate statistical analysis is an analysis that is conducted on a primary outcome measure, in response to an FDA request. In the same section, we correct an error that suggested that the submission of statistical analysis information applied only to the information in proposed § 11.48(a)(3)(v)(C). Additional elaboration is also provided on the information required to be submitted as a brief description of each arm/group (a similar omission was described for § 11.48(a)(1) and (a)(2)). We remove the requirement to submit Outcome Measure Reporting Status (see proposed § 11.48(a)(3)(iii)(E)) because a more streamlined approach makes this item obsolete (*i.e.,* the submission of Measure Type and Measure of Dispersion or Precision, Unit of Measure, and Outcome Measure Data are sufficient for determining that Outcome Measure Information and Outcome Measure Data are intended to be posted). We explain how to specify, as part of Outcome Measure Data, whether the number of participants (or units) analyzed in a category differs from the overall Number of Participants Analyzed and Number of Units Analyzed in § 11.48(a)(3)(ii). We have also updated the options available for specifying the type of statistical test in the Statistical Analysis Overview as well as the Measure Type and Measure of Dispersion or Precision (includes additional options for counts of participants or units and for specifying a confidence interval). Finally, minor changes have been made for consistency with similar data items in Demographic and baseline characteristics in § 11.48(a)(2). Final § 11.48(a)(3) otherwise retains the following outcomes and statistical analyses information as proposed: (i) Outcome Measure Arm/Group Information, (ii) Analysis Population Information, (iii) Outcome Measure Information, (iv) Outcome Measure Data, and (v) Statistical Analyses.

As discussed in Section IV.B.4 of this preamble, primary and secondary outcome measures are submitted as part of the registration process. *ClinicalTrials.gov* was designed to display the results of each outcome measure in separate tables organized by arm or comparison group. The responsible party determines the rows and columns for each outcome measure table; columns represent arms or comparison groups, and rows represent data categories (*e.g.,* for categorical data types). The responsible party populates the table cells with data from the clinical trial. Attributes such as measure type (*e.g.,* mean), measure of dispersion or precision (*e.g.,* standard deviation), and unit of measure (*e.g.,* milliseconds) provide context for interpreting the numerical data. In this way, the system can accommodate either continuous or categorical data, as desired by the responsible party based on the design and analysis of the clinical trial as specified in the protocol and SAP. For example, time-to-event data could be provided as either a continuous measure (*e.g.,* median time to response) or as categorical data (*e.g.,* number of participants with response by year 5).

In order to enhance the ability of users to understand and interpret the submitted clinical trial results information and help ensure that submitted information is complete, § 11.48(a)(3)(i)–(v) requires the responsible party to submit information for completing a table of data for each primary and secondary outcome measure, by arm or comparison group, including the results of scientifically appropriate tests of the statistical significance. This is done by submitting the following information, which is used to create and populate the outcome data tables:

(1) Outcome Measure Arm/Group Information, which is described in § 11.48(a)(3)(i) as ''[a] brief description of each arm or comparison group used for submitting an outcome measure for the clinical trial, including a descriptive title to identify each arm or comparison group.'' As discussed in Section IV.C.4 of this preamble on Demographic and baseline characteristics, this information describes the grouping of human subjects for the purposes of analysis, whether by arm of the clinical trial or another comparison group. *ClinicalTrials.gov* will use the Arm Information, Intervention Name, and Intervention Description data elements (submitted as clinical trial registration information), as well as Participant Flow Arm Information and Baseline Characteristics Arm/Group Information, to provide the responsible party with options for pre-populating table column names and descriptions for Outcome Measure Arm/Group Information. The responsible party must review and edit the information as needed to ensure that it appropriately and accurately reflects the outcome measure arms/groups for the clinical trial, or the responsible party may instead define new groups to reflect how outcome measure information was analyzed. As described in the discussion of the term ''comparison group'' in § 11.10(a) of the preamble, the reference to comparison groups recognizes that when data collected during clinical trials are analyzed, the data are often aggregated into groupings of human subjects (*i.e.,* comparison groups) other than the arms to which the subjects were assigned for the study. It is expected that Outcome Measure Arm/Group Information will be the same as Participant Flow Arm Information, unless human subjects were analyzed in groups different from those to which they were assigned. In this situation, there must be sufficient details for users to understand how the arm(s) or comparison groups used for submitting outcome measures were derived from Participant Flow Arm Information. In general, the Outcome Measure Arm/Group Information must be inclusive of all arms or comparison groups, based on the pre-specified protocol and/or SAP. The Outcome Measure Arm/Group Information must also include sufficient details for users to understand the intervention strategy being described in that arm/group, similar to what is described in this preamble for Participant Flow Arm Information in § 11.48(a)(1).

(2) Analysis Population Information, as described in § 11.48(a)(3)(ii), consists of the following: (A) Number of Participants Analyzed, (B) Number of Units Analyzed, and (C) Analysis Population Description. Number of Participants Analyzed means ''[t]he number of human subjects for whom an outcome was measured and analyzed, by arm or comparison group.'' If the analysis is based on a unit other than participants (*e.g.,* lesions, eyes, implants), the responsible party is also required to provide the Number of Units Analyzed, which is defined as ''. . . a description of the unit of analysis and the number of units for which an outcome was measured and analyzed, by arm or comparison group.'' In addition, if the Number of Participants Analyzed or Number of Units Analyzed in an arm or comparison group differs from the number of human subjects or units assigned to the arm or comparison group, the responsible party is also required to provide an Analysis Population Description, which is explained as ''a brief description of the reason(s) for the difference.'' For example, if some participants assigned to arms drop out before one of the outcome measures is assessed or if some participants are otherwise ineligible for analysis, the responsible party would include an explanation in the Analysis Population Description. Similarly, if a clinical trial enrolled participants but was terminated before outcome measure data were collected, the entry would explain why the Number of Participants Analyzed is zero even though

participants had been assigned to the relevant arm or comparison group.

(3) Outcome Measure Information, as described in § 11.48(a)(3)(iii), includes the following components: (A) Name of the specific outcome measure, including the titles of any categories into which Outcome Measure Data in § 11.48(a)(3)(iv) are aggregated; (B) Description of the metric used to characterize the specific outcome measure; (C) Time point(s) at which the measurement was assessed for the specific metric; (D) Outcome Measure Type, which indicates whether the outcome measure is one of the following types of outcome measures: primary, secondary, other pre-specified, or post-hoc; (E) Measure Type and Measure of Dispersion or Precision, which indicates the type of data submitted and the measure of dispersion or precision; and (F) Unit of Measure (*e.g.,* blood pressure in ''millimeters of mercury'' or ''participants''). As described Section IV.B.4 of this preamble for § 11.28(a)(2)(i)(W) and (X), when an attribute such as blood pressure is summarized using more than one metric or method of aggregation (*e.g.,* mean and median) and/or summarized at more than one time point (*e.g.,* 3 months, 6 months, 9 months), each of these is considered a different outcome measure. In addition, the description of the time point(s) of assessment must be specific to the submitted outcome measure and is generally the specific duration of time over which each human subject is assessed (not the overall duration of the trial). As described in this section of this preamble for Baseline Measure Information, when responsible parties submit information using categories, they may indicate which information type is being reported (participants in mutually exclusive and exhaustive categories or a list of items for which participants may be represented in more than one row) to allow for improved options for data validation (*e.g.,* the system can ensure that the sum of participants in mutually exclusive and exhaustive categories is the same as Number of Participants Analyzed).

In specifying the type of data to be submitted as part of Measure Type and Measure of Dispersion or Precision, the responsible party is required to select one option from the following limited list of options for Measure Type: ''count of participants,'' ''count of units,'' ''number,'' ''mean,'' ''median,'' ''least squares mean,'' ''geometric mean,'' and ''geometric least squares mean.'' In specifying the Measure of Dispersion or Precision, the responsible party is required to select one option from the following limited list of options: ''standard deviation,'' ''standard error,'' ''inter-quartile range,'' ''full range,'' ''geometric coefficient of variation'' (which is permitted only if the specified Measure Type is ''geometric mean'' or ''geometric least squares mean''), ''not applicable'' (which is permitted only if the specified Measure Type is ''count of participants,'' ''count of units,'' ''number''), ''80% confidence interval,'' ''90% confidence interval,'' ''95% confidence interval,'' ''97.5% confidence interval,'' ''99% confidence interval,'' and ''other confidence interval level'' (which must also include a specification of the numerical value of the confidence interval level). There is no general ''other'' option for either the Measure Type or Measure of Dispersion or Precision entries, but responsible parties may optionally provide additional descriptive information as part of the free-text Outcome Measure Description. Collecting Measure Type and Measure of Dispersion or Precision in this format improves the ability of users' to compare submitted information across clinical trials and also ensures complete data submission. For example, if the responsible party indicates that the measure of dispersion is inter-quartile range, *ClinicalTrials.gov* can prompt the submission of the two values corresponding to the upper and lower bounds of the inter-quartile range, instead of only the single value needed to submit a standard deviation. Unit of Measure describes what is quantified by the data (*e.g.,* blood pressure in ''millimeters of mercury'' or ''participants''). Each outcome measure can only have one unit of measure.

In most cases, Name of the specific outcome measure, Description of the metric, Time point(s), and Outcome Measure Type (§ 11.48(a)(3)(iii)(A), (B), (C), and (D)) for the primary and secondary outcome measures would have been submitted at the time of clinical trial registration, as specified in § 11.28(a)(2)(i)(W) and (X), and updated during the course of the clinical trial, as specified in § 11.64. Final § 11.64(a) specifically requires responsible parties to update information submitted during registration at the time they submit results. To ensure consistent data entry and reduce the data entry burden on responsible parties, *ClinicalTrials.gov* will automatically pre-populate the results data tables with the previously submitted (and updated) registration information and will allow the responsible party to make further updates as necessary or desired (*e.g.,* to provide clarification that would enable users to better interpret the submitted results values). If data were not collected for an outcome measure in a clinical trial (*i.e.,* Number of Participants Analyzed in all arms or comparison groups is zero for that outcome measure), the responsible party is not required to submit Measure Type and Measure of Dispersion or Precision and Unit of Measure (§ 11.48(a)(3)(iii)(E) and (F)) for that outcome measure, as no Outcome Measure Data in § 11.48(a)(3)(iv) would be submitted. This situation may occur, for example, if a clinical trial is terminated before data are collected for a pre-specified primary or secondary outcome measure.

(4) Outcome Measure Data, which is described in § 11.48(a)(3)(iv), consists of ''[t]he measurement value(s) for each outcome measure for which data are collected, by arm or comparison group and by category (if specified).'' The information provided for Outcome Measure Data must use the Unit of Measure and correspond to the Measure Type and Measure of Dispersion or Precision submitted as described in § 11.48(a)(3)(iii)(E) and (F). In addition, the responsible party may specify the number of participants (and units, if applicable), by arm or comparison group, if different in any category from the Number of Participants Analyzed or Number of Units Analyzed in § 11.48(a)(3)(ii)(A) or (B).

(5) Statistical Analyses are specified in § 11.48(a)(v) as the ''[r]esults of scientifically appropriate tests of the statistical significance of the primary and secondary outcome measures, if any.'' In implementing this requirement, we clarify the meaning of ''scientifically appropriate'' as it relates to Statistical Analyses for the purposes of this regulation only. In this final rule, we specify in § 11.48(a)(3)(v)(A) that a statistical analysis is required to be submitted if it meets any one of the following three criteria in the context of a particular applicable clinical trial:

- A statistical analysis that is pre-specified in the protocol and/or SAP and was performed on primary or secondary outcome measure data. Statistical analyses that are pre-specified in the protocol for a primary or secondary outcome measure, but are considered exploratory, are excluded from these requirements.
- A statistical analysis for a primary or secondary outcome measure that is made public by the sponsor or responsible party, where ''made public'' is considered to be when the statistical analysis is available in written form (*e.g.,* journal publication, scientific abstract, press release). We believe that the decision by the sponsor or responsible party to publicly disseminate a statistical analysis for a

primary or secondary outcome measure implicitly indicates that an assessment of the scientific appropriateness of the analysis has been made. The fact that the Agency is adopting this approach in the regulation does not reflect the Agency's agreement that such statistical analyses are necessarily scientifically valid. Recognizing that the time at which an analysis is made public and the submission requirements under this rule may not overlap, this criterion is limited to analyses made public before clinical trial results information is submitted for the primary outcome measure(s) studied in the clinical trial.

• A statistical analysis conducted on a primary outcome measure in response to a request made by FDA. We limit the requirement regarding FDA-requested statistical analyses to those analyses requested by FDA for a primary outcome measure prior to the submission of clinical trial results information for all primary outcome measures. This avoids requiring a responsible party to submit FDA-requested analyses if such analyses would be based on results information that was submitted to *ClinicalTrials.gov* prior to FDA's request.

Statistical analyses that meet any of these criteria must be submitted to *ClinicalTrials.gov* at the time of results or partial results information submission. In addition, we clarify that these criteria apply only to statistical analyses that rely on information and data that are specified as primary or secondary outcome measure information in § 11.48(a)(3)(i)–(iv). This limitation is necessary because statistical analyses are only interpretable in the context of the summary outcome measure information that forms the basis for the analysis. These criteria, therefore, do not have the effect of requiring a responsible party to submit primary or secondary outcome measure information in § 11.48(a)(3)(i)–(iv) that is not otherwise required to be submitted.

We specify in § 11.48(a)(3)(v)(B) that the information that a responsible party must submit for statistical analyses of primary and secondary outcome measures is as follows:

(1) Statistical Analysis Overview, which identifies the arms or comparison groups compared in the statistical analysis (by selecting the arms or comparison groups already defined for the outcome measures) and specifies the type of analysis conducted. The type of analysis conducted would be selected from the following limited set of options: ''superiority,'' ''non-inferiority,'' ''equivalence,'' or ''other'' (which must also include a description of the analysis type). The ''other'' option would be appropriate for a single group analysis or other descriptive statistics, for example. If the type of analysis selected is ''non-inferiority'' or ''equivalence,'' the responsible party is also required to provide a free-text description of key parameters of the statistical analysis to include, at minimum, information about the power calculation and the non-inferiority or equivalence margin. An additional comment field is offered to provide the responsible party with the opportunity to submit optional additional information about the statistical analysis.

(2) The Responsible Party must provide either the Statistical Test of Hypothesis or the Method of Estimation, as applicable. If the statistical analysis performed cannot be submitted using the Statistical Test of Hypothesis or Method of Estimation options, a general ''other'' option is available for submitting any other scientifically appropriate tests of statistical significance. Statistical Test of Hypothesis consists of the p-value and the procedure used for statistical analysis of the outcome data. For convenience in specifying the procedure used for the statistical analysis, *ClinicalTrials.gov* includes the following list of commonly used statistical tests for calculating p-values from which responsible parties may select: ''ANCOVA;'' ''ANOVA;'' ''Chi-squared;'' ''Chi-squared, Corrected;'' ''Cochran-Mantel-Haenszel;'' ''Fisher Exact;'' ''Kruskal-Wallis;'' ''Log Rank;'' ''Mantel Haenszel;'' ''McNemar;'' ''Mixed Models Analysis;'' ''Regression, Cox;'' ''Regression, Linear;'' ''Regression, Logistic;'' ''Sign Test;'' ''t-Test, 1-sided;'' ''t-Test, 2-sided;'' and ''Wilcoxon (Mann-Whitney).'' Responsible parties may also select the ''other'' option and provide the name of another method. Additional comment fields are available to provide the responsible party with an opportunity to submit optional additional information about the statistical test of hypothesis, such as a description of the null hypothesis, adjustments for multiple comparisons, a priori thresholds for statistical significance, and degrees of freedom. Method of Estimation consists of the estimation parameter, estimated value, and confidence interval (if calculated). For convenience in describing Method of Estimation, *ClinicalTrials.gov* includes the following list of more than a dozen commonly used estimation parameters from which responsible parties may select: ''Cox Proportional Hazard;'' ''Hazard Ratio (HR);'' ''Hazard Ratio, log;'' ''Mean Difference (Final Values);'' ''Mean Difference (Net);'' ''Median Difference (Final Values);'' ''Median Difference (Net);'' ''Odds Ratio (OR);'' ''Odds Ratio, log;'' ''Risk Difference (RD);'' ''Risk Ratio (RR);'' ''Risk Ratio, log;'' and ''Slope.'' Responsible parties may also select the ''other'' and provide the name of another estimation parameter. If a confidence interval was calculated, the responsible party will submit the confidence level, indicate whether the confidence interval is one-sided or two-sided, and provide the upper and/or lower limits of the confidence interval. A responsible party could specify that the confidence interval is one-sided and provide only the upper or lower limit. If one of the limits of a two-sided confidence interval cannot be calculated, the responsible party is required to specify that limit as ''Not Available'' and provide a brief narrative explanation (*e.g.,* because an insufficient number of clinical trial participants reached the event at the final time point for assessment). A responsible party may also submit, on an optional basis, a dispersion value. If a dispersion value is submitted, the responsible party is required to specify the parameter of dispersion by selecting one of the following options: ''standard deviation'' or ''standard error of the mean.'' No ''other'' option for the parameter of dispersion is available. An additional comment field is available to provide the responsible party with an opportunity to submit optional additional information about the method of estimation, such as the direction of the comparison (*e.g.,* for a relative risk). The requirements for submitting statistical analysis information attempt to balance the benefits of structured data with minimal narrative text with the need to describe what was evaluated in the statistical analysis. For the reasons discussed in section III.C., in addition to the information specified above, responsible parties also have the option of voluntarily submitting additional, free-text information in order to provide a more complete description of the statistical analyses. This free-text information should not include an interpretation of results or conclusions, just a description of the statistical test(s) conducted. Submitted statistical analyses are linked to each submitted outcome measure. Although a responsible party is not limited in the number of statistical analyses that can be submitted for each outcome measure, only statistical analyses that rely on submitted outcome measure information

and data can be described. Specifically, the requirement is limited to statistical analyses that rely on the summary outcome information and data submitted, including Outcome Measure Arm/Group Information, Analysis Population Information, Outcome Measure Information, and Outcome Measure Data. Statistical analyses that use data external to the clinical trial or different analysis populations or are limited to certain sub-groups would generally not meet this requirement unless, for example, the summary sub-group data were submitted as part of the primary or secondary outcome measure (*e.g.,* using categories or comparison groups).

In specifying requirements for outcome measures and statistical analyses under § 11.48(a)(3), two situations merit further clarification. The first involves a clinical trial terminated before data are collected for one or more of the pre-specified outcome measures. Certain information is still required to be submitted for outcome measures for which data were not collected. Under § 11.48(a)(3)(ii) the responsible party would be required to submit the Number of Participants Analyzed, which would be zero (''0'') for an outcome measure for which no data were collected. The responsible party is not required to submit the Measure Type and Measure of Dispersion or Precision, and Unit of Measure data elements specified in § 11.48(a)(3)(iii)(E) and (F), for any outcome measure for which data were not collected but would be required to provide the other elements of Outcome Measure Information specified in § 11.48(a)(3)(iii)(A), (B), (C), and (D). As specified in § 11.48(a)(3)(iv), the responsible party is not required to submit Outcome Measure Data for the outcome measure(s) for which no data were collected but is required to submit Outcome Measure Data for any other primary and secondary outcomes for which data were collected. For terminated trials, the responsible party must still meet the requirements specified in § 11.48(a)(1), (2), and (4) for the submission of results information for the Participant Flow, Demographic and baseline characteristics, and Adverse event information modules. If a clinical trial enrolls no participants, the information to be updated for the Enrollment data element under § 11.64(a) would be zero (''0'') and no results information would be required to be submitted for that clinical trial.

The second situation involves a clinical trial for which outcome measures are collected but the actual enrollment falls well below the target enrollment. This could occur, for example, if a clinical trial is terminated due to poor enrollment after only some participants are enrolled but outcomes are measured. Even in such situations, collected results information must be submitted to *ClinicalTrials.gov* as specified in this rule (taking into account the privacy considerations discussed in section III.C.16 of the NPRM preamble (79 FR 69591) if actual enrollment is very small). The submission and posting of results information for such a clinical trial would be consistent with section 402(j) of the PHS Act and provide a way of tracking the progress of the clinical trial and demonstrating what happened to the human subjects who were enrolled. If the clinical trial was terminated because of safety concerns or efficacy, the results information would be of considerable interest to users interested in human health and safety information. In order to reduce the chances that users of *ClinicalTrials.gov* might misinterpret submitted results information, we encourage the responsible party to submit additional optional information about the clinical trial in the Analysis Population Description data element and/or in the Limitations and Caveats module of *ClinicalTrials.gov.* This additional information could highlight that enrollment in the clinical trial did not reach the target number of subjects needed to achieve target power and was insufficient to produce statistically reliable results. If the trial was terminated, the posted study record will clearly reflect that the trial was terminated (*i.e.,* the responsible party indicates Overall Recruitment Status as ''terminated''), and we intend to include information on the posted study record to allow the public to easily see when actual enrollment was below the target enrollment goals (using information from the Enrollment data element and submitted expected and actual values). We believe that this information will make it easier for the public to consistently identify across studies when a trial was terminated and/or actual enrollment was below the target enrollment goals. We expect that, in most of these situations, no statistical analysis information would be submitted for the affected outcome measure(s) because no statistical analyses would have been performed or would be considered scientifically appropriate.

§ 11.48(a)(4)—Adverse Event Information

Overview of Proposal

The proposal for submitting adverse event information in § 11.48(a)(4) was based on the information required to complete the two tables specified as additional results information in sections 402(j)(3)(I)(iii)(I) and (II) of the PHS Act, with modifications to further assist users in understanding and interpreting submitted adverse event information. Specifically, section 402(j)(3)(I)(i) of the PHS Act requires the Secretary, by regulation, to ''determine the best method for including in the registry and results data bank appropriate results information on serious adverse and frequent adverse events for applicable clinical trials . . . in a manner and form that is useful and not misleading to patients, physicians, and scientists.'' Section 402(j)(3)(I)(ii) of the PHS Act specifies that if regulations are not issued by the date that is 24 months after the date of the enactment of FDAAA (*i.e.,* by September 27, 2009), the requirement to submit results information necessary to complete the two tables specified in sections 402(j)(3)(I)(iii)(I) and (II) of the PHS Act would take effect as stated in section 402(j)(3)(I)(ii). The statutorily mandated adverse event reporting provisions require the submission of two tables of information, as follows: (1) ''[a] table of anticipated and unanticipated serious adverse events grouped by organ system, with number and frequency of such event in each arm of the clinical trial'' (section 402(j)(3)(I)(iii)(I) of the PHS Act), referred to hereinafter as the ''serious adverse events table'' and (2) ''[a] table of anticipated and unanticipated adverse events that are not included in the [serious adverse events table] . . . that exceed a frequency of 5 percent within any arm of the clinical trial, grouped by organ system, with number and frequency of such event in each arm of the clinical trial'' (section 402(j)(3)(I)(iii)(II) of the PHS Act). In the NPRM and in the *ClinicalTrials.gov* data bank, we refer to adverse events that do not fit the definition of a serious adverse event as ''other adverse events,'' and we refer to the adverse events table in item (2) above as the ''other adverse events table'' (79 FR 69588).

Consistent with this section of the PHS Act, the Agency proposed in § 11.48(a)(4)(i) to require ''[i]nformation for completing two tables summarizing adverse events collected during an applicable clinical trial: (A) Table of all serious adverse events, grouped by organ system, with the number and

frequency of each event by arm or comparison group; (B) Table of all adverse events, other than serious adverse events, that exceed a frequency of 5 percent within any arm of the clinical trial, grouped by organ system, with the number and frequency of each event by arm or comparison group.'' Proposed § 11.48(a)(4)(ii) further specified that information for each table must include the following: (A) Adverse Event Arm/Comparison Group Information; (B) Total Number Affected by Arm or Comparison Group; (C) Total Number at Risk by Arm or Comparison Group; (D) Total Number Affected by Organ System; (E) Total Number at Risk by Organ System; (F) Adverse Event Information, to include a descriptive term for the adverse event and organ system associated with the adverse event; (G) Adverse Event Data, to include for each adverse event the number of human subjects affected and at risk; and (H) Additional Adverse Event Description. The NPRM also indicated in proposed § 11.48(a)(4)(iii) that information provided by organ system must be grouped using the organ system classification established on *ClinicalTrials.gov.* These data elements (with the exception of the new Total Number Affected by Organ System and Total Number at Risk by Organ System data elements) were first made available in September 2008 as optional data elements; they became required as of September 27, 2009. The Additional Adverse Event Description data element has been available as an optional data element since September 2008 (named Adverse Event Reporting Additional Description) with the following other optional data elements: Time Frame for Adverse Event Reporting, Assessment Type (*i.e.,* collection approach), Source Vocabulary Name (for specifying a standard vocabulary), and Number of Events (for number of occurrences of an adverse event). The NPRM proposal and request for comment on additional data elements was also based on our operational experience with adverse event information since 2008.

In section III.C.15 of the NPRM, we requested comments on all aspects of the proposed requirements for submission of adverse event information. This included considerations of the following: (1) Benefit and burden of the proposed modifications to the statutorily mandated adverse event reporting provisions (*i.e.,* number of participants affected and at risk for adverse events at the organ system level); (2) benefit and burden of additional information considered but not included in the proposal, including the time frame for collecting adverse events, the collection approach (systematic or non-systematic), all-cause mortality information, a standard vocabulary for submitted adverse event terms, number of occurrences of an adverse event and attribution of an adverse event to the intervention(s) under study; (3) ways to reduce the data submission burden without reducing the value of the data; and (4) approaches to increasing standardization in the vocabularies used for adverse event information (79 FR 69591). The Agency also specifically requested comments on whether the organ system classification is sufficient and whether additional categories or an ''other'' option are necessary (79 FR 69644).

Comments and Response

Most of the commenters who addressed the requirements for adverse event information were generally supportive of the requirements that were consistent with current practice and the statutorily mandated adverse event reporting provisions. Some commenters expressed support for the proposal for adverse event information, including the submission of additional information and the data elements on adverse events on which we sought comment. One commenter expressed overall support for the proposal but generally indicated that it is a change from current practice in academic medical centers and expressed concern about the burden of the requirements. Many commenters addressed issues related to specific data elements and opposed the proposal to require the submission of adverse event information aggregated by the total number of participants affected and at risk for adverse events for each organ system. Commenters expressed opposition to these requirements because they considered the requirements to be beyond the statutorily mandated adverse event reporting provisions and they questioned the Agency's legal authority to require information not specified in those provisions.

We first address the general issue of the Agency's legal authority to require adverse event information not specified in the statutorily mandated adverse event reporting provisions. The adverse event information proposed to be required in § 11.48(a)(4) is based on the provisions in sections 402(j)(3)(I)(iii)(I) and (II) of the PHS Act, with some modifications. We interpret the provision as providing the Secretary with authority to modify the required information, by regulation, under section 402(j)(3)(D)(v)(VI) of the PHS Act, which specifies that the regulations shall establish ''additions or modifications to the manner of reporting of the data elements established under [section 402(j)(3)(C) of the PHS Act].'' Section 402(j)(3)(I)(v) of the PHS Act deems adverse event information to be ''clinical trial information included in [the] data bank pursuant to . . . [section 402(j)(3)(C) of the PHS Act].'' We also interpret that this clinical trial information is therefore included in the ''data elements established under . . . [section 402(j)(3)(C) of the PHS Act]'' referred to in section 402(j)(3)(D)(v)(VI) of the PHS Act. Therefore, we conclude that the Secretary has the authority, under section 402(j)(3)(D)(v)(VI) of the PHS Act, to modify the statutorily mandated adverse event reporting provisions for the submission of adverse event information via regulation, because such modifications represent ''additions or modifications to the manner of reporting [adverse event information] . . .''

The modifications to the statutorily mandated adverse event reporting provisions in this final rule represent modifications to the ''manner of reporting'' required adverse event information. As described above, section 402(j)(3)(D)(v)(VI) of the PHS Act authorizes the Secretary to make ''additions or modifications to the manner of reporting of the data elements established under [section 402(j)(3)(C) of the PHS Act]'' by regulation. We interpret the ''manner of reporting of the data elements'' to include specific content requirements for reporting information in the categories of information under section 402(j)(3)(C) of the PHS Act. For example, section 402(j)(3)(C) of the PHS Act identifies certain content requirements for data elements, such as ''Primary and Secondary Outcomes.'' If the ''manner of reporting of the data elements established under [section 402(j)(3)(C) of the PHS Act]'' does not include the content requirements for these categories, then ''additions or modifications'' would be strangely limited to changing only how the information must be submitted (*e.g.,* on paper or electronically), not what information must be submitted. This interpretation would leave us in the untenable situation, which we believe was not Congress' intent, of having to limit ''additions or modifications'' to changes only in *how* information must be submitted, not to *what* information must be submitted. Section 402(j)(3)(I)(i) of the PHS Act also informs this question by directing the Secretary within 18 months to determine by

regulation ''the best method for including in the registry and results data bank appropriate results information on serious adverse and frequent adverse events . . . in a manner and form that is useful and not misleading to patients, physicians, and scientists.'' Because the ''manner'' and ''form'' must be ''useful and not misleading,'' it would not be reasonable to conclude that such regulations could only specify the means of submitting and displaying the adverse event information, but not the information content. Finally, we believe Congress intended the Agency to have broad rulemaking authority to add to the information requirements of the data bank, as demonstrated in section 402(j)(3)(D)(i) of the PHS Act, which directs that the data bank be expanded by rulemaking ''[t]o provide more complete results information and to enhance patient access to and understanding of the results of clinical trials.'' In this section, we explain the modifications made to the statutorily mandated adverse event reporting provisions and clarify how these modifications represent ''additions or modifications to the manner of reporting'' adverse event information.

Commenters were concerned about the burden of providing adverse event information aggregated by the total number of participants affected and at risk for adverse events for each organ system, particularly for studies at academic medical centers and, in general, because this information is not routinely summarized for adverse events occurring during a trial. Some were concerned about adverse event data being reported differently on *ClinicalTrials.gov* as compared to EMA, FDA labeling, and other summary reports available on the FDA Web site (*e.g.,* 510(k) summary). One commenter was supportive of the proposal only if it meant that all participants affected by an adverse event (whether serious or not) would be summarized by system organ class. Having considered the comments, the Agency is not including a requirement in this final rule to submit the total number of participants affected and at risk for adverse events by organ system. This data element was proposed as a new requirement; it was not part of other adverse event data elements that were implemented in 2009 as optional or required information. The comments helped us understand the extent to which such information is not routinely aggregated in this manner and the potential burdens associated with the requirement. We note that, in general, there will be differences between the information reported on *ClinicalTrials.gov* and in other reports, such as those submitted to FDA, because of differences in the underlying statutory framework and the requirements of the related regulations and elaborations provided in guidance.

There were comments on the proposal to provide adverse event information by system organ class, based on the use of an organ system classification established in *ClinicalTrials.gov.* Most of these comments were in the context of the proposed requirement to summarize the total number of participants affected and at risk for adverse events for each organ system, which is not included in the final rule. The NPRM preamble described this organ system classification as based on the Medical Dictionary for Regulatory Affairs (MedDRA) [Ref. 99] (79 FR 69589) As a standardized medical terminology, MedDRA is used internationally for the reporting of drug and biologic regulatory information and was adopted by ICH [Ref. 100]. Commenters indicated that at academic institutions there are not institution-wide systems established for the collection of adverse event information in a standard manner that would include MedDRA's organ system classification and that investigator-sponsors may not have access to MedDRA. In addition, commenters indicated that the requirements should be kept simple and ''consistent with current practice.'' One commenter requested an extended transition period for ongoing studies to allow for the incorporation of MedDRA into their processes. Some commenters also requested implementation of a new PRS feature to assist investigators who are responsible parties in classifying adverse events using MedDRA system organ classes. Although the final rule no longer includes the proposal to require the total number of participants affected and at risk by organ system, there is still a requirement to provide, for each adverse event, the ''[o]rgan system associated with the adverse event.''

The proposal to require this organ system information is derived from the statutorily mandated adverse event reporting provisions that specified that adverse events need to be ''grouped by organ system.'' The organ system classification used to describe a specific adverse event submitted to *ClinicalTrials.gov* has been based on MedDRA organ system classes since the adverse events module was made available in September 2008 (and was required in September 2009). Thus, the final rule is consistent with current practice. Our experience indicates that responsible parties are able to use these classes effectively and that a single set of organ system classes provides a consistent way to display information about adverse events among the tables for a single trial and across trials. We also note that there are publicly available resources for mapping to MedDRA system organ classes, such as the NCI's thesaurus [Ref. 101], ''a widely recognized standard for biomedical coding and reference, used by a broad variety of public and private partners both nationally and internationally including the Clinical Data Interchange Standards Consortium Terminology (CDISC), the U.S. Food and Drug Administration (FDA), the Federal Medication Terminologies (FMT), and the National Council for Prescription Drug Programs (NCPDP).'' In the final rule, to clarify the circumstances in which the organ system is relevant, we have removed the general provision from the codified that stated that the information ''must be grouped according to the organ system classification established in *ClinicalTrials.gov.*'' Instead, when submitting the organ system associated with the adverse event, as specified in final § 11.48(a)(4)(iii)(D)(2), the responsible party is required to select one option describing the organ system from a list of options established on *ClinicalTrials.gov.* This approach improves consistency with other data elements in which the format (also described in Section IV.A.4) is to select from menu options. The use of this particular list for organ system class is based on our experience with voluntary and mandatory adverse events submission since September 2008, which indicates that responsible parties are able to use these classes effectively and that a single set of organ system classes provides a consistent way to display information about adverse events among the tables for a single trial and across trials.

Two commenters indicated that, for certain trials of devices, the protocol specifies adverse event reporting only for organ systems that may be affected by the device. We note that we do not intend for these regulations to result in requiring an investigator to collect adverse event information of any type or in any way that is not specified in the protocol. Therefore, if adverse events were collected for only some organ systems, as pre-specified in the protocol, the responsible party would need to submit only those adverse events to *ClinicalTrials.gov.* The Additional Adverse Events Description data element (renamed ''Adverse Event

Reporting Description'' in the final rule) could be used to describe the methods for adverse event collection, including any organ system classes that were not evaluated. We also note that since the publication of the NPRM, MedDRA version 19.0 was released, which includes a new system organ class called ''product issues.'' We will add this to the classification on *ClinicalTrials.gov,* bringing the total number of organ system classes to 27. Although we requested comments on whether an ''other'' option is necessary for the organ system class, no specific comments were received.

Commenters requested that instead of the proposed requirement to report other adverse events that exceed a frequency of 5 percent within any arm of the clinical trial, the final rule require all other adverse events to be reported (*i.e.,* other adverse events that exceed a frequency of 0 percent). These commenters were concerned that the 5 percent threshold for reporting other adverse events did not have a clear scientific basis and potentially would allow some findings to go unreported. Similarly, one commenter requested that ''all adverse events occurring in five percent or more of patients across arms receiving the investigational product'' be required to be reported, based on a concern that if there are multiple arms with the investigational product, the overall frequency of adverse events among participants receiving the investigational product may be higher than 5 percent. Another commenter suggested that the 5 percent threshold could be used for differentiating expected and unexpected adverse events. Our proposal for reporting anticipated and unanticipated other adverse events that exceed a frequency of 5 percent within any arm of the trial is based on section 402(j)(3)(I)(iii)(II) of the PHS Act. As stated in the NPRM (79 FR 69588), we will allow the submission of other adverse events with a frequency of 5 percent or less on an optional basis, as many responsible parties are currently doing. This allows responsible parties to determine whether a threshold of 5 percent or less is scientifically appropriate for their study. We believe that this approach strikes an appropriate balance between the potential burden of reporting all adverse events for all applicable clinical trials and the scientific value of allowing responsible parties to report adverse events occurring below the 5 percent threshold for a particular clinical trial. If a responsible party chooses to report adverse events that occur at a lower frequency (*i.e.,* 5 percent or less), the specific threshold must be identified (*e.g.,* 3 percent) and used for reporting all adverse events in each arm of the trial. This approach helps avoid the type of reporting bias that occurs when the reporting threshold varies by adverse event or by arm. Similarly, not permitting the threshold to be higher than 5 percent, which is consistent with section 402(j)(3)(I)(iii)(II) of the PHS Act, avoids another type of reporting bias that could occur if the threshold was allowed to be set at any value (*i.e.,* higher thresholds in some trials but not others could exclude the submission of important adverse event information). Therefore, we maintain the approach described in the NPRM to require the reporting of all other adverse events, other than serious adverse events, that exceed a frequency of 5 percent within any arm of the clinical trial.

We invited comments on the benefits and burdens of requiring additional adverse event information, including time frame, collection approach, all-cause mortality information, and a standard vocabulary for adverse event terms (79 FR 69590). Some commenters were in favor of adding a requirement to submit the adverse event reporting time frame; one reason given was that the provision of this information would help avoid inappropriate comparisons across clinical trials that used different time frames. We agree that the time frame is important for comparing information across trials, and we note that it is also important for interpreting clinical trial results information within the context of a single trial, since the time frames for data collection for primary outcome measures, secondary outcome measures, and adverse events may all be different. Similarly, we note that § 11.44(d) describes partial results information submission deadlines based on when final data collection occurs for primary outcome measures, secondary outcome measures, and additional adverse event information. In this context, it is particularly important to have a description of the adverse event reporting time frame so that it is clear what time frame for assessment applies to adverse event information submitted as partial results. In the NPRM, we noted that responsible parties provided time frame information for more than half of the results information submitted in 2012 for probable applicable clinical trials (79 FR 69590). (See the explanation of probable applicable clinical trial in section IV.B.2). In 2015, nearly 60 percent of results submitted for probable applicable clinical trials included information for the time frame data element. Based on the current use of this data element and the implications for interpreting adverse event information in the context of a single clinical trial and across trials, we are adding adverse event reporting time frame as a requirement in the final rule. As explained in detail earlier in this section, we consider this required information to represent a modification to the ''manner of reporting'' in section 402(j)(3)(D)(v)(VI) of the PHS Act; the information helps elucidate the adverse event information in the statutorily mandated reporting provisions.

Commenters who addressed the issue of collection approach for adverse event information were generally in favor of adding a requirement to submit this information, suggesting that such contextual information is important for interpreting the benefits and harms of an intervention evaluated in a trial and for comparing adverse event information across trials. Collection approach information includes an indication of the type of approach taken to collect adverse event information, either a systematic assessment or a non-systematic assessment. In the NPRM, we explained that a ''systematic assessment'' involves the use of a specific method of ascertaining the presence of an adverse event (*e.g.,* the use of checklists, questionnaires,specific laboratory tests at regular intervals), and a ''non-systematic assessment'' relies on the spontaneous reporting of adverse events, such as unprompted self-reporting by participants (79 FR 69590). [Ref. 102] One commenter suggested that the information be provided in a free-text field (instead of as a binary indication) to allow the responsible party to describe how adverse events were collected and adjudicated. We acknowledge that this can be a complex issue; however, we believe that the binary, structured indication of either a systematic or non-systematic assessment provides users of *ClinicalTrials.gov* with a consistent way of understanding what was done in the clinical trial. We also note that the free-text field for Adverse Event Reporting Description can be used by the responsible party to describe the methods for adverse event collection and provide any further details about adjudication. The submission of the protocol, as described in § 11.48(a)(5), also would typically provide additional supporting information that is important for interpreting the collection approach and the submitted adverse event information. Another commenter requested clarification ''on the classification of routine investigator assessment of adverse events (when an

investigator asks if the subject has had an adverse event) as a Systematic Assessment.'' We interpret this routine investigator assessment to mean that the investigator asks a general question about whether a participant had any adverse events at prespecified intervals, rather than more targeted questions about specific categories or types of adverse events. We clarify that such a routine, general assessment would be considered a ''non-systematic assessment.'' However, if more specific questions were asked about adverse events at regular intervals, this approach could be considered a ''systematic assessment.'' We agree with the commenters that knowledge of the collection approach affects comparability of information across clinical trials and we believe that such information is similarly important for interpreting adverse event information for a single clinical trial. As we noted in the NPRM, clinical trials using non-systematic assessment approaches typically record fewer adverse events than those using a systematic assessment approach [Ref. 102]. We also noted in the NPRM that, of the results for probable applicable clinical trials submitted to *ClinicalTrials.gov* in 2012, 76 percent voluntarily included information about the approach to collecting adverse events (79 FR 69590). In 2015, reporting was about the same, with 74 percent of results submitted for probable applicable clinical trials including information on the collection approach for adverse events. Based on the current use of this data element and the importance of this information for interpreting adverse event information, we require this information in the final rule. As explained in detail earlier in this section, this required information constitutes a modification to the ''manner of reporting'' in section 402(j)(3)(D)(v)(VI) of the PHS Act; this information helps elucidate the adverse event information in the statutorily mandated adverse event reporting provisions.

Commenters who addressed the topic of including all-cause mortality information supported requiring the submission of such information, with the exception of one commenter. Commenters who supported the requirement stated that accurate information about the number of deaths in each arm of the clinical trial was critical for interpreting the trial's results. One of these commenters suggested that it would be misleading to have a statement specific to all-cause mortality information that explains that deaths may not be related to the intervention evaluated because this is actually what randomized trials are designed to understand. In addition, if there were such a statement, it would apply equally to other results, including outcomes. Some commenters (including some who supported the requirement) expressed concern about the interpretation of all-cause mortality information, particularly in the absence of information about attribution (*i.e.,* whether the deaths were considered related to the intervention). The commenter opposed to the requirement expressed concern that the reporting of all-cause mortality information would increase the risk of re-identification of participants in the clinical trial, leading to requests for waivers of the clinical trial results information submission requirements, but the commenter did not provide further explanation of how the risk of re-identification would increase.

We have considered these comments and require in the final rule the submission of all-cause mortality information in addition to the serious adverse events and other adverse events tables. This required information constitutes a modification to the ''manner of reporting'' in section 402(j)(3)(D)(v)(VI) of the PHS Act; this information helps elucidate the adverse event information in the statutorily mandated adverse event reporting provisions. Specifically, although other clinical trial results information may include information about deaths, the total number of deaths that occurred during the clinical trial might not be readily apparent (*e.g.,* submitted serious adverse event information indicates the number of subjects who experienced a myocardial infarction, but it would not necessarily indicate how many of the subjects died from the event).

As noted in the NPRM, submission of all-cause mortality information would be consistent with other clinical trial reporting guidelines (79 FR 69590) [Ref. 56, 103]. The all-cause mortality information is described in § 11.48(a)(4)(ii) of the final rule as being provided by the responsible party in a separate table. This approach allows the responsible party to use the Adverse Event Arm/Group Information as the table columns and, for each arm/group (*i.e.,* separate column), to specify the overall number of human subjects affected by death due to any cause and the overall number of human subjects included in the assessment as a table row. The information will then be displayed as a row in the serious adverse events table in the posted study record. As with serious and other adverse event information, we will make available an optional data element for providing descriptive information that the responsible party deems appropriate.

We acknowledge the concerns expressed by some of the commenters about potential misinterpretation of adverse event information. To address those concerns, we intend to provide standard explanatory information on each posted record that will help the public understand the definition of ''all-cause mortality'' and that will further explain that all-cause mortality information, serious adverse events, and other adverse events appearing on *ClinicalTrials.gov* are generally reported regardless of attribution. Similarly, in the context of all results information, a standard statement on the posted record will indicate that results of a single clinical trial may not be representative of the overall efficacy and safety profile of the product and that the FDA-approved product labeling should be consulted for information for approved drug products (including biological products) and device products. In response to the comment about waivers, we note that the NPRM indicated that a high risk of re-identification would be an appropriate reason for requesting that the requirement for submitting all-cause mortality information be waived, using the process described in proposed § 11.54. However, because adverse event information is summary data provided in aggregate, we expect that waivers would be requested and granted in a very limited number of situations.

Comments were mixed on the issue of whether attribution of an adverse event to a specific intervention evaluated in a study should be provided. Some commenters were opposed to providing information about attribution because of a lack of consensus about the optimal methodology for making such determinations, leading to concerns about the potential for tremendous variability and subjectivity across clinical trials regarding how decisions about attribution were made. Commenters indicated that attribution can only be assessed after a trial is completed (*e.g.,* by comparing rates of events across arms of the clinical trial), and even then, decisions about attribution based on a single clinical trial may be incorrect. Similarly, one of these commenters cited FDA guidance to reviewers that instructs them to ''discount'' attribution information [Ref. 104]. One commenter suggested that because of the challenges in correctly assigning attribution, such information should be prohibited. One commenter suggested that a disclaimer be added to adverse event information to explain

that the data do not necessarily reflect a conclusion by the sponsor or FDA that the event was caused or contributed to by the intervention. Some commenters were in favor of the submission of attribution information because they thought it was necessary to prevent misunderstandings about the safety of study interventions, including devices, and the risks of trial participation. One commenter indicated that the requirements for adverse event submission should be limited to only those serious adverse events and adverse events considered related to the intervention. In addition to the concerns raised by the commenters, we note that providing information on attribution would add an additional burden on responsible parties. Given the challenges described by commenters in accurately assigning attribution within the context of a single clinical trial, as well as similar concerns that we raised in the NPRM (79 FR 69589), we are not including attribution information in the final rule. We recognize that the monitoring of adverse events during a clinical trial has an important role in identifying the risks and benefits for human subjects participating in the clinical trial. [Ref. 105]. Attempts to determine attribution of an intervention to each individual adverse event, however, may be subjective (and potentially misleading), particularly after study completion when aggregate adverse event information is available to make objective quantitative assessments of the potential attribution of the intervention to the adverse event. [Ref. 106, 107, 108]. As noted in the discussion for all-cause mortality, we intend to include a standard statement on *ClinicalTrials.gov* to help the public understand that all-cause mortality information, serious adverse events, and other adverse events are generally reported regardless of attribution. We received one comment in support of requiring the submission of the number of occurrences of an adverse event (in addition to the number of participants affected by the adverse event). This optional data element has been available to responsible parties since the adverse events module was released in September 2008, and we will continue to make it available as an optional data element.

A few commenters addressed the topic of whether we should require the submission of adverse event terms using a standard vocabulary. One of the commenters was opposed, citing in particular the burden that would be imposed if that particular vocabulary had not been used in a trial from the outset. Another commenter recommended that a standard vocabulary for adverse events be used, noting that emerging technologies could potentially take advantage of standard terminologies. We also interpret many of the comments received on using the MedDRA classification system for summarizing the total number of participants affected and at risk for adverse events by organ system as opposition to requiring a specific vocabulary. We did not receive any other suggested approaches for standardizing the vocabularies used for adverse event information. Taking into consideration the burden and the potential for this requirement to cause a responsible party to report or collect adverse event information in any way that is not specified in the protocol, we do not include in the final rule a requirement to submit adverse event terms using a standard vocabulary. We will, however, continue to provide optional data elements to allow responsible parties to describe the standard vocabulary that was used, if applicable.

We also received some comments in response to our request for additional input on ways to reduce the data submission burden without reducing the value of the data. Commenters requested tools (in addition to XML) for uploading datasets for the adverse event tables. In the preamble of this final rule describing the format required for submitting clinical trial information in § 11.8, we note that the PRS has allowed the submission of adverse event information in a spreadsheet format (*e.g.,* Microsoft Excel) since 2013. We will continue to support uploading of adverse event information that uses this format and meets the technical specifications.

Some commenters suggested that the regulations explicitly state that only adverse event information collected ''per protocol'' is required to be submitted. The requirements in the final rule are not intended to cause an investigator to collect information of a type or in a way not specified in the protocol. However, situations may arise during the conduct of a trial in which the responsible party collects and reports certain relevant adverse events that were not anticipated in the protocol and/or that occur in participants thus not following the protocol. Therefore, we maintain the proposed language in the final rule (*i.e.,* ''collected during'') to cover all relevant situations. But we reiterate that the requirements in the final rule do not impose data collection requirements for an applicable clinical trial. One commenter suggested that adverse event information requirements should be less rigorous for products not being conducted under an IND/IDE because the safety and efficacy has already been established. We do not agree that the reporting of adverse event information for clinical trials not being conducted under an IND/IDE should be less rigorous. We believe that the purpose of the *ClinicalTrials.gov* database to make information available to the public is best achieved by requiring the same adverse event reporting requirements for all applicable clinical trials.

Final Rule

Final § 11.48(a)(4) generally maintains the NPRM approach, but we are making the following changes in the final rule: First, we remove the proposed requirement that the overall number of participants affected and at risk, by arm or comparison group, be reported by organ system class. Second, we add a requirement to submit all-cause mortality information by arm or comparison group. Third, we add a requirement to provide the time frame for adverse event data collection. Fourth, we add a requirement to provide the collection approach (systematic or non-systematic) for adverse events. In addition, in developing the final rule we have identified a few issues that would benefit from further clarification, based on our operational experience and routine queries from users. Specifically, we are clarifying the additional information required to be provided including a brief description of each arm/group (a similar omission was described for § 11.48(a)(1), (2), and (3)). We have renamed the proposed Additional Adverse Event Description data element to ''Adverse Event Reporting Description'' and included it as § 11.48(4)(i)(B) with the other requirements added in the final rule (*i.e.,* Time Frame and Collection Approach) that also pertain to information about methods for adverse event collection. In addition, this name change is intended to reduce the potential for misinterpreting the data element as relating to a specific adverse event, rather than to definitions related to adverse event reporting overall. The change also better aligns the name of this data element with the optional data element in place on *ClinicalTrials.gov* prior to the final rule.[Ref. 97]. In addition, minor changes have been made for consistency with terms used in the statute and with similar data items in Demographic and baseline characteristics specified in § 11.48(a)(2) and Outcomes and statistical analyses in § 11.48(a)(3).

Final § 11.48(a)(4) requires the submission of summary information on anticipated and unanticipated adverse events that occurred during an applicable clinical trial. This includes a table of all serious adverse events; a table of adverse events other than serious adverse events that exceed a frequency of 5 percent within any arm of the clinical trial; and a table of all-cause mortality information, which will be displayed as a row in the serious adverse event table. Such information is considered part of results information. The requirements derive from the statutorily mandated adverse event reporting provisions in sections 402(j)(3)(I)(ii)–(iii) of the PHS Act and include the following additional requirements intended to assist users in understanding and interpreting the submitted adverse event information: Arm/group description, adverse event reporting description, time frame, collection approach, and all-cause mortality information.

We interpret modifications to the ''manner of reporting'' in section 402(j)(3)(d)(v)(VI) of the PHS Act to include, among other things, information that helps elucidate the adverse event information required by the statutorily mandated adverse event reporting provisions. The definitions of ''adverse event'' and ''serious adverse event'' are provided in § 11.10(a).

Final § 11.48(a)(4)(i) requires the responsible party to submit information that describes the methods for collecting adverse event information. The Time Frame data element, as specified in § 11.48(a)(i)(A), describes the time period over which the submitted adverse event information was collected as well the overall period of time for which additional adverse event information was, is being, or will be collected (*e.g.,* primary outcome measure data and adverse events collected over the same time period as the primary outcome are submitted, but secondary outcome measure and additional adverse event data collection is ongoing). Similar to the information provided for outcome measures on the time points of assessment (§ 11.48(a)(3)(iii)(C)), the time frame for adverse event reporting is generally the specific duration of time over which each human subject is assessed for adverse events. Time frame information is a ''manner of reporting'' adverse event information and helps elucidate the adverse event information required by the statutorily mandated adverse event reporting provisions.

In cases in which the protocol specifies the collection of only a limited set of adverse events (*e.g.,* unanticipated adverse reactions), the responsible party is still required to submit three tables of information that summarize the information collected during the clinical trial with respect to serious adverse events, other adverse events (other than serious adverse events) that exceed a frequency of 5 percent within any arm of the trial, and all-cause mortality. The all-cause mortality information will be displayed as a row in the serious adverse event table. As specified in § 11.48(a)(4)(i)(B), if the adverse event information collected in the trial is collected based on a definition of ''adverse event'' and/or ''serious adverse event'' that is diffrerent from the definitions in § 11.10(a), the responsible party must use the Adverse Event Reporting Description data element to explain the differences. Similarly, the responsible party must use the Adverse Event Reporting Description data element to explain whether these definitional differences include adverse event collection methods that exclude certain types of adverse events required to be reported in § 11.48(a)(4) (*e.g.,* protocol specified that other adverse events are not to be collected, only serious adverse events are collected). This explanation facilitates the understanding of required adverse event information in situations where different definitions or methods of collection are used. Adverse Event Reporting Description constitutes a ''manner of reporting'' adverse event information that facilitates understanding the nature of the events being reported. Responsible parties may also use the Adverse Event Reporting Description data element, on an optional basis, to provide general information that they deem important for explaining methods of adverse event collection and reporting, including additional details about the collection approach.

Collection Approach, specified in § 11.48(a)(i)(C), allows the responsible party to identify whether a ''systematic assessment'' or ''non-systematic assessment'' approach was taken to collect adverse event information during the trial. Responsible parties must specify the assessment type for adverse event information as a whole or for each adverse event in each table. Systematic assessment involves the use of a specific method of ascertaining the presence of an adverse event (*e.g.,* the use of checklists, questionnaires, or specific laboratory tests at regular intervals). Non-systematic assessment relies on spontaneous reporting of adverse events, such as unprompted self-reporting by participants. This information explains how the statutorily mandated adverse event information was obtained and constitutes a ''manner of reporting'' this information authorized to be required by section 402(j)(3)(D)(v)(VI) of the PHS Act. We note that the requirements are not intended to cause an investigator to collect adverse event information of any type or in any way not specified in the protocol.

Final § 11.48(a)(4)(ii) specifies that responsible parties must submit three tables summarizing information on all serious adverse events, other adverse events with a frequency higher than 5 percent in any arm or comparison group of the clinical trial, and all-cause mortality. Final § 11.48(a)(4)(iii) specifies that there must be a description of each arm or comparison group for which adverse event information was collected and the overall number of human subjects affected by and at risk must be described for each of the following tables: (1) Serious adverse events, (2) adverse events other than serious adverse events that exceed a frequency threshold of 5 percent within any arm, and (3) deaths due to any cause. We note that the death of a human subject could be reflected in information included in the serious adverse event table and in the all-cause mortality table. For example, a death separately identified in the serious adverse event table with a descriptive term for the adverse event such as ''myocardial infarction'' (as specified § 11.48(a)(4)(iii)(D)(1)) would also be included in the overall number of human subjects affected in the all-cause mortality table. The all-cause mortality information required by this rule is simply another meaningful way to aggregate and report one important type of serious adverse event (*i.e.,* those that led to death). The all-cause mortality information is a ''manner of reporting'' the adverse event information authorized to be required by section 402(j)(3)(D)(v)(VI) of the PHS Act.

The arm and comparison group information is provided once by the responsible party and is used for all three tables. As similarly discussed in this section under Demographic and baseline characteristics and Outcomes and statistical analyses, the Adverse Event Arm/Group Information data element describes the grouping of human subjects for the purposes of summarizing adverse event information. These descriptions are necessary to understand the statutorily mandated adverse event reporting information. Adverse Event Arm/Group Information is another ''manner of reporting'' the

adverse event information authorized to be required by section 402(j)(3)(D)(v)(IV) of the PHS Act. *ClinicalTrials.gov* will use the Arm Information, Intervention Name, and Intervention Description data elements (submitted as clinical trial registration information), as well as Participant Flow Arm Information, Baseline Characteristics Arm/Group Information, and Outcome Measure Arm/Group Information, to provide the responsible party with options for pre-populating table column names and descriptions for Adverse Event Arm/Group Information. The responsible party must review and edit the information as needed to ensure that it appropriately and accurately reflects the adverse event arms/groups for the clinical trial, or the responsible party may instead define new groups to reflect how adverse event information was analyzed. As described in the discussion of the term ''comparison group'' in § 11.10(a) of the preamble, the reference to comparison group recognizes that when data collected during clinical trials are analyzed, the data are often aggregated into groupings of human subjects (*i.e.,* comparison groups) other than the arms to which the subjects were assigned for the study. It is expected that Adverse Event Arm/Group Information will be the same as Participant Flow Arm Information, unless human subjects were analyzed in groups that are different from those to which they were assigned. In this situation, there must be sufficient detail to understand how the arm(s) or comparison groups used for submitting adverse events were derived from Participant Flow Arm Information. In general, Adverse Event Arm/Group Information must be inclusive of all arms or comparison groups, based on the pre-specified protocol and/or SAP. Adverse Event Arm/Group Information must also include sufficient details to understand the intervention strategy being described for that arm/group, similar to that which is described in § 11.48(a)(1) for Participant Flow Arm Information.

For each of the serious and other adverse events tables described in § 11.48(a)(4)(ii)(A) and (B), respectively, the responsible party must provide a descriptive term for each serious adverse event and other adverse event with a frequency higher than 5 percent in any arm of the clinical trial (§ 11.48(a)(4)(iii)(D)(*1*)), along with the organ system that is associated with the adverse event (§ 11.48(a)(4)(iii)(D)(*2*)), number of participants experiencing the adverse event (§ 11.48(a)(4)(iii)(E)(*1*)), and number of participants at risk for the adverse event (§ 11.48(a)(4)(iii)(E)(*2*)). In most cases, the number of participants at risk for the adverse event will equal the number of participants who started that arm of the clinical trial. However, the number of participants at risk could differ if, for example, participants were assigned to an arm but did not receive the intervention (*e.g.,* because they dropped out of the clinical trial) or because a comparison group combines participants from multiple arms of the trial. The number of participants at risk for each adverse event will generally be the same as the overall number of participants at risk in the arm or comparison group. To minimize the burden of data entry, the overall number of participants at risk will be pre-populated for each adverse event term. However, if these numbers are not the same (*e.g.,* certain adverse events were only systematically evaluated in a sub-group of human subjects enrolled in the clinical trial), the responsible party can modify the number of participants at risk for each adverse event, as needed. Using the data submitted for the number of participants that experienced the adverse event and the number of participants at risk, *ClinicalTrials.gov* will automatically calculate the frequency (percentage of participants who experienced the event). This approach helps reduce calculation errors and helps users interpret the frequency information in those cases in which the full study population may not have been at risk for a specific adverse event or when the number of participants at risk is different across comparison groups.

Adverse events described in § 11.48(a)(4)(iii)(D)(*1*) must be submitted with an indication of the organ system associated with the adverse event (as described in § 11.48(a)(4)(iii)(D)(*2*)) using the classification scheme specified on *ClinicalTrials.gov,* which includes the following 27 items adapted from the MedDRA version 19.0: Blood and lymphatic system disorders; Cardiac disorders; Congenital, familial and genetic disorders; Ear and labyrinth disorders; Endocrine disorders; Eye disorders; Gastrointestinal disorders; General disorders; Hepatobiliary disorders; Immune system disorders; Infections and infestations; Injury, poisoning and procedural complications; Investigations; Metabolism and nutrition disorders; Musculoskeletal and connective tissue disorders; Neoplasms benign, malignant and unspecified (including cysts and polyps); Nervous system disorders; Pregnancy, puerperium and perinatal conditions; Product issues; Psychiatric disorders; Renal and urinary disorders; Reproductive system and breast disorders; Respiratory, thoracic and mediastinal disorders; Skin and subcutaneous tissue disorders; Social circumstances; Surgical and medical procedures; and Vascular disorders organ classes [Ref. 99]. No ''other'' option is included. ''Product issues'' is not an organ class (like most of the other categories), but this term is used in MedDRA for issues with ''product quality, devices, product manufacturing and quality systems, supply and distribution, and counterfeit products'' [Ref. 109]. ''Social circumstances'' is also not an organ class but is used in MedDRA to accommodate the classification of some types of adverse events that are not specific to an organ system, such as an automobile accident, a homicide, or a fall. Adverse events that affect multiple systems must be reported only once (to avoid over-counting), preferably under the organ system class that is considered primary. If there is no primary organ system class, the event should be listed under ''General disorders,'' and additional information may be provided in the optional free-text field, Adverse Event Term Additional Description.

Finally, we note that the Agency interprets section 402(j)(3)(I)(v) of the PHS Act to deem the adverse event information required under section 402(j)(3)(I) of the PHS Act as clinical trial results information not only for all applicable clinical trials but also for all voluntarily-submitted clinical trials under section 402(j)(4)(A) of the PHS Act. Therefore, responsible parties who submit clinical trial information subject to section 402(j)(4)(A) of the PHS Act must submit adverse event information in accordance with § 11.48(a)(4). Additional information on the clinical trial information requirements for voluntarily-submitted clinical trials under section 402(j)(4)(A) of the PHS Act, is described in Section IV.D.1.

§ 11.48(a)(5)—Protocol and Statistical Analysis Plan

Section 11.48(a)(5) adds a requirement to submit the protocol and statistical analysis plan as part of clinical trial results information. The proposal, comments and response, and final rule requirements are discussed in detail in Section III.D.

§ 11.48(a)(6)—Administrative Information

Overview of Proposal

Proposed § 11.48(a)(5)(i) implemented section 402(j)(3)(C)(iii) of the PHS Act,

which requires that ''a point of contact for scientific information about the clinical trial results'' be submitted as part of clinical trial results information, and specified the submission of the following information to allow users of *ClinicalTrials.gov* to inquire about the results of a clinical trial: (1) Name or official title of the point of contact, (2) name of affiliated organization, and (3) telephone number and email address of the point of contact (79 FR 69644). This proposal reflects the Results Point of Contact data element used on *ClinicalTrials.gov* since the results database was first launched in September 2008 [Ref. 97].

Proposed § 11.48(a)(5)(ii) implemented section 402(j)(3)(C)(iv) of the PHS Act, which requires responsible parties to indicate ''whether there exists an agreement . . . between the sponsor or its agent and the principal investigator . . . that restricts in any manner the ability of the principal investigator, after the primary completion date of the trial, to discuss the results of the trial at a scientific meeting or any other public or private forum, or to publish in a scientific or academic journal information concerning the results of the trial.'' The statutory provision also provides that this requirement does not apply to an agreement between a sponsor or its agent and the principal investigator solely to comply with applicable provisions of law protecting the privacy of participants in the clinical trial. We explained in the proposed rule preamble that in accordance with proposed § 11.48(a)(5)(ii), we required responsible parties to indicate (yes/no) whether the principal investigator is an employee of the sponsor. If the principal investigator is an employee of the sponsor (yes), no further information must be provided, although it may be provided voluntarily. If the principal investigator is not (no), the responsible party would be required to indicate (yes/no) whether an agreement (other than one solely to comply with applicable provisions of law protecting the privacy of human subjects participating in the clinical trial) exists between the sponsor or its agent and the principal investigator that restricts in any manner the ability of the principal investigator, after the primary completion date of the clinical trial, to discuss the results of the clinical trial at a scientific meeting or any other public or private forum or to publish in a scientific or academic journal information concerning the results of the clinical trial. We also proposed to permit responsible parties to provide additional optional information about existing agreements. The proposal reflected the Certain Agreements data element used on *ClinicalTrials.gov* since the results component of the database was first launched in September 2008 [Ref. 97]. We invited public comment on the proposed approach, on any experience to date with the current approach, and on other information that might be collected on a voluntary basis (*e.g.,* types of principal investigator disclosure restrictions) (79 FR 69644).

Comments and Response

Regarding the results point of contact in proposed § 11.48(a)(5)(i), a few commenters suggested that the final rule not require the submission and posting of information that would identify an individual employee. One commenter proposed to instead require a general facility email address or contact form. We generally agree with these comments and note that the proposed approach, which is retained in the final rule, did not require the disclosure of an individual's name or specific contact information, but permitted the use of an official title and a general organizational phone number or email address. While the name of a specific individual and contact information for that individual are not required, a responsible party must provide sufficient information to allow users to reach a contact able to provide additional scientific information about the clinical trial results found on a posted record.

Some commenters addressed the certain agreements provision in proposed § 11.48(a)(5)(ii). One commenter suggested the addition of another category to the existing three optional choices currently available on *ClinicalTrials.gov,* to help viewers understand restrictions related to multi-site trials. For example, a sponsor may limit or prohibit individual-site principal investigators from disclosing single-site results before the overall results aggregated from all sites of a multi-center trial are disclosed. Another commenter proposed that such agreements be nullified in the event that clinical trial information submitted by a sponsor without the consent or knowledge of the principal investigator is found to be misrepresented or in the event of any legal proceedings arising from false or misleading data. In response to the first commenter, the Agency will consider the suggestion when deciding in the future whether to modify or restructure the optional principal investigator Disclosure Restriction Type component of the Certain Agreements data element. In response to the second commenter, the legal status of agreements between a sponsor or its agent and the principal investigator is outside the scope of this rulemaking. Final § 11.48(a)(6)(ii) provides the mechanism for mandatory reporting of the existence of such agreements for applicable clinical trials under this part.

Final Rule

Taking into consideration the commenters' suggestions and the statutory requirements for the submission of additional components of clinical trial results information, the final rule maintains the approach proposed in § 11.48(a)(5). Final § 11.48(a)(6)(i) requires the submission of the following information for a point of contact for scientific information about the results information for a clinical trial: Name or official title, name of the affiliated organization, and the telephone number and email address. We note that point of contact information is required to be submitted even if it is the same as the information for the responsible party, because we do not plan to make public the responsible party's contact information.

Final § 11.48(a)(6)(ii) requires the submission of information about certain agreements between the principal investigator and the sponsor. The responsible party must indicate whether the principal investigator is an employee of the sponsor. If the principal investigator is not an employee, the responsible party must indicate whether any agreement exists that restricts the principal investigator from disclosing the results of the clinical trial after the primary completion date. Consistent with the definition of ''principal investigator'' in § 11.10, we interpret this provision as applying to a principal investigator who has oversight of the entire applicable clinical trial, not to site-specific investigators or other investigators (such as those on grant-funded studies) who may be referred to as principal investigators in other contexts but who do not meet the definition of ''principal investigator'' under this part. We clarify that when the responsible party for a clinical trial is a sponsor-investigator, for the purposes of submitting information about certain agreements in § 11.48(a)(6)(ii), we interpret that the sponsor-investigator is both the sponsor and the principal investigator and is therefore considered an employee of the sponsor for the purposes of this section. We also clarify that the information about certain agreements that is required to be submitted under this regulation must accurately represent the status at the time of initial results

information submission, and if that information has changed since the previous submission of partial clinical trial results information, the responsible party must submit information to reflect the new status of certain agreements between the principal investigator and the sponsor at the time of the subsequent submission of partial results information, in accordance with § 11.44(d)(3)(ii). For example, if the principal investigator had been an employee of the sponsor prior to results information submission but is no longer employed by the sponsor at the time of initial results information submission, the principal investigator would not be considered an employee of the sponsor for the purposes of submitting partial results information about certain agreements. However, if the principal investigator's employment status subsequently changes and he or she becomes an employee of the sponsor prior to the submission of final results information, the certain agreements information would need to be included when submitting partial results information as specified in § 11.44(d)(3)(ii). Note that the Certain Agreements results data element specified in § 11.48(a)(6)(ii) is excluded from the update requirements specified in § 11.64(a)(2).

Additionally, in our interactions with responsible parties and consultations with stakeholders, we have learned that certain agreements of the nature described in section 402(j)(3)(C)(iv) of the PHS Act are routine in the clinical trials community, although they may vary in their terms and the duration of their limitations on the principal investigator. Such agreements, as we understand them, typically permit the sponsor or its delegate to review results communications prior to public release and impose a short-term embargo of 60 days or less, from the date that the communication is submitted to the sponsor for review, although other agreements may impose restrictions that are much longer in duration or broader in scope [Ref. 110]. In order to allow responsible parties to provide additional information about the agreements in place between the sponsor or its delegate and the principal investigator, we permit the submission of optional, structured information about the agreement. These optional data elements, which are separate and distinct from the two data elements required as part of clinical trial results information, as previously discussed, are: (1) Whether the principal investigator is an employee of the sponsor and, if not, (2) whether any agreement exists that restricts the principal investigator from discussing or publishing the results of the clinical trial after the primary completion date. Thus, currently on *ClinicalTrials.gov,* a responsible party who wishes to provide this additional information may choose from among the following:

(1) The only disclosure restriction on the principal investigator is that the sponsor can review results communications prior to public release and can embargo communications regarding clinical trial results for a period that is less than or equal to 60 days from the date that the communication is submitted to the sponsor for review. The sponsor cannot require changes to the communication and cannot unilaterally extend the embargo.

(2) The only disclosure restriction on the principal investigator is that the sponsor can review results communications prior to public release and can embargo communications regarding clinical trial results for a period that is more than 60 days but less than or equal to 180 days from the date that the communication is submitted to the sponsor for review. The sponsor cannot require changes to the communication and cannot unilaterally extend the embargo.

(3) Other disclosure agreement that restricts the right of the principal investigator to disclose, discuss or publish clinical trial results after the trial is completed. The responsible party may provide an additional description of the disclosure agreement.

Based on our experience operating *ClinicalTrials.gov,* the usage of these optional responses suggests that they provide an acceptable way to describe these agreements in a consistent format. These categories of optional information may be modified over time to reflect information that we learn about changes in clinical trials practice or to provide other information of interest to users. As permitted by law, we may make these changes without notice and comment rulemaking. However, we will provide prior notice and seek public comment on any proposed changes of a substantive nature to the format of required results information submission information (see § 11.8 and the discussion in Section IV.A.4 of this preamble).

§ 11.48(a)(7)—Additional Clinical Trial Results Information for Applicable Device Clinical Trials of Unapproved or Uncleared Device Products

Overview of Proposal

Proposed § 11.48(a)(6)(i) enumerated additional descriptive information that responsible parties would need to submit as part of the clinical trial results information for applicable device clinical trials of unapproved or uncleared devices for display on the posted record. For applicable device clinical trials of unapproved or uncleared devices subject to delayed posting of registration information in proposed § 11.35(b)(2)(i), the results information specified in proposed § 11.48(a)(1) through (5) can be submitted as specified in proposed § 11.44(c) and publicly posted as required by proposed § 11.52 *prior* to the date on which clinical trial registration information is publicly posted (79 FR 69645).

In proposing § 11.48(a)(6)(i), we exercised the authority granted under sections 402(j)(3)(D)(ii)(II) and 402(j)(3)(D)(iii) of the PHS Act to require responsible parties of applicable device clinical trials of unapproved or uncleared devices to submit, as part of results information, certain additional descriptive information that is similar to the type of information submitted at the time of registration. In particular, section 402(j)(3)(D)(ii)(II) of the PHS Act authorizes the Secretary to determine through rulemaking whether responsible parties for applicable clinical trials of unapproved products would be subject to the results information submission requirements under proposed subpart C. Additionally, section 402(j)(3)(D)(iii)(IV) of the PHS Act grants the Secretary wide discretion in determining what information can be required through rulemaking to be submitted as part of results information, stating that the regulations ''shall require, in addition to the elements described in [section 402(j)(3)(C)] . . . [s]uch other categories as the Secretary determines appropriate.'' Therefore, the Secretary can require, through rulemaking, submission of not only the results information required under section 402(j)(3)(C) of the PHS Act, but also ''such other categories'' of information as the Secretary determines appropriate. We noted in the NPRM that we interpret ''such other categories'' of results information for applicable device clinical trials of unapproved or uncleared device products to include, among other things, certain descriptive information that is similar to the type of information required to be submitted

under section 402(j)(2)(A)(ii) of the PHS Act. We pointed out that if clinical trial registration information is not available until after the posting of results information, users of *ClinicalTrials.gov* would lack access to certain descriptive information necessary to enhance access to and understanding of, the submitted results information and to determine whether the required results information has been submitted (*e.g.,* for all arms of the study). Therefore, this descriptive information, as a component of clinical trial results information for unapproved or uncleared devices, would be posted based on the timeline specified in § 11.52 (79 FR 69645).

To make submission of the necessary descriptive information easier and to reduce the risk of inconsistency or error, § 11.48(a)(6)(ii) proposed to require responsible parties to affirm the accuracy of the descriptive information that is similar to the type of information submitted when the trial is registered by verifying and updating it as necessary and then affirming that this descriptive information is ready to be posted with the results information. Once affirmed, the proposed rule explained, *ClinicalTrials.gov* would automatically populate the clinical trial results descriptive information data elements using the previously submitted clinical trial registration elements that are similar to the type of information to be submitted when the trial is registered. The proposed approach would decrease the burden on responsible parties, reduce inconsistencies between information previously submitted at registration and information submitted with results, and increase administrative efficiency by reducing the need for the Agency to conduct a wholly-new quality control review of the submitted information (79 FR 69645).

Comments and Response

We did not receive any specific comments about the proposal to require additional descriptive results information for applicable device clinical trials of unapproved or uncleared devices in proposed § 11.48(a)(6). We did receive comments concerning the submission of any results information for unapproved or uncleared devices, and these comments are addressed in Section III.B. of this preamble.

Final Rule

Final § 11.48(a)(7)(i) specifies the additional results information necessary to enhance access to and understanding of the results of applicable clinical trials of unapproved or uncleared device products consistent with the proposed rule. However, this section clarifies that this requirement is limited to applicable clinical trials of unapproved or uncleared device products for which clinical trial registration information has not been posted publicly by the Director on *ClinicalTrials.gov* in accordance with § 11.35(b)(2)(i). This section also includes minor modifications to the names of data elements for consistency with modifications to the data elements in § 11.10(b). Additionally, final § 11.48(a)(7) clarifies that ''device'' means ''device product.''

Final § 11.48(a)(7)(ii) states that responsible parties must submit all the results information specified in § 11.48(a)(7)(i). We clarify that this applies to all applicable device clinical trials of unapproved or uncleared device products that are subject to § 11.48(a)(7)(i), regardless of when the trial was initiated. We also clarify that if a responsible party indicates to the Director that it is authorizing the Director, in accordance with § 11.35(b)(2)(ii), to publicly post its clinical trial registration information on *ClinicalTrials.gov* prior to the date of FDA approval or clearance of the device product, the applicable device clinical trial of its unapproved or uncleared device product is not subject to § 11.48(a)(7)(i).

Section 11.48(a)(7)(ii) additionally requires responsible parties to submit an affirmation that any information previously submitted to *ClinicalTrials.gov* for the data elements listed in paragraph § 11.48(a)(7)(i) of this section have been updated in accordance with § 11.64(a) and are to be included as clinical trial results information. As described above, to make submission of the necessary descriptive information under § 11.48(a)(7)(i) easier and to reduce the risk of inconsistency or error, *ClinicalTrials.gov* will automatically populate the clinical trial results descriptive information data elements using the previously submitted clinical trial registration elements that are similar to the type of information submitted when the trial is registered. This automatic population approach is intended to decrease the burden on responsible parties, reduce inconsistencies between information previously submitted and information submitted with results, and increase administrative efficiency. The affirmation in § 11.48(a)(7)(ii) therefore applies to the previously submitted information that will be used to populate the data elements listed in § 11.48(a)(7)(i). The responsible party must enter any additional descriptive information that has not been automatically populated, as § 11.48(a)(7)(ii) requires the submission of all results information specified in § 11.48(a)(7)(i).

§ 11.48(b)—Results Information for a Pediatric Postmarket Surveillance of a Device Product That Is Not a Clinical Trial

Overview of Proposal

Proposed § 11.48(b) specified the results information that must be submitted to *ClinicalTrials.gov* for a pediatric postmarket surveillance of a device that is not a clinical trial. We proposed that the final report submitted to FDA according to 21 CFR 822.38 (or any successor regulation) must be submitted to *ClinicalTrials.gov* in a common electronic document format and must include redactions of personally identifiable information and commercial confidential information. We invited public comment on the proposed approach (79 FR 69646).

Comments and Response

Commenters addressed the proposal for a pediatric postmarket surveillance of a device that is not a clinical trial in proposed § 11.48(b). Commenters recommended that the final rule alternatively allow for the submission of a study summary in place of a redacted final report, suggesting that the redacted final report ''might be confusing and virtually unreadable.'' One commenter indicated that a pediatric postmarket surveillance of a device that is not a clinical trial should be required to provide the same clinical trial results information (as for a clinical trial) identified in proposed § 11.48(a). As noted in the NPRM, ''pediatric postmarket surveillances under section 522 of the FD&C Act can take various forms [other than a clinical trial], including a detailed review of the complaint history and the scientific literature, non-clinical testing, observational studies . . .'' (79 FR 69576). As such, it may not always be possible or appropriate for the responsible party for a pediatric postmarket surveillance of a device that is not a clinical trial to provide all of the specified results data elements or data tables required for clinical trials in proposed § 11.48(a). Regarding the suggested submission of a study summary, it is not clear, based on the comments, which specific items would be included in such a summary and how the components could be described in the context of this final rule. Because of the broad spectrum of types of studies that may be considered pediatric

postmarket surveillances of a device, it is not possible to fully elucidate the items that should be present in such a summary that would apply to all types of studies. On the other hand, the final report submitted to FDA would include the results information that was deemed important by FDA. Therefore, we maintain the approach in the final rule that the responsible party is required to provide a copy of the final report submitted to FDA. This approach ensures that the information and requirements are consistent for all types of pediatric postmarket surveillances of a device product that are not clinical trials. We have, however, modified the requirement as described in the NPRM, in that we are not requiring that the final report be redacted. Upon further consideration, we believe that it is appropriate to leave decisions about information to be redacted to the discretion of the responsible party.

Final Rule

Taking into consideration the commenters' suggestions and the statutory requirements for the submission of clinical trial results information for a pediatric postmarket surveillance of a device that is not a clinical trial, we maintain in the final rule the approach proposed in § 11.48(b), but we remove the requirement to redact information from the final report submitted to FDA and clarify that ''device'' means ''device product.''

Final § 11.48(b) specifies the results information that must be submitted to *ClinicalTrials.gov* for a pediatric postmarket surveillance of a device product that is not a clinical trial. We recognize that a pediatric postmarket surveillance of a device product may take any of several forms, including prospective surveillance studies and historical reviews of the health records of those who have received a device as an intervention, and may not meet the definition of a ''clinical trial'' under this part. For this reason, it is not possible to specify particular data elements or tables of data for all types of pediatric postmarket surveillances of a device product that are not clinical trials. For each pediatric postmarket surveillance of a device product that is not a clinical trial, the final report submitted to FDA according to 21 CFR 822.38 (or any successor regulation) is required to be submitted to *ClinicalTrials.gov*. The responsible party may redact names, addresses, and other personally identifiable information, as well as any proprietary information (*i.e.,* trade secrets and/or confidential commercial information) contained in the report, but the redacted information should not include any of the information required to be submitted under §§ 11.28(a) or 11.48(a) of this part. The final report is required to be submitted in a common electronic document format specified on *ClinicalTrials.gov* at *https://prsinfo.clinicaltrials.gov* (or successor site).

5. § 11.52—By when will the NIH Director post submitted clinical trial results information?

Overview of Statutory Provisions and Proposal

According to section 402(j)(3)(G) of the PHS Act, for applicable clinical trials, the Director of NIH is required to post results information ''publicly in the registry and results database not later than 30 days after such submission.'' Proposed § 11.52 implemented this provision, stating that NIH will post publicly ''clinical trial results information submitted under this subpart at *ClinicalTrials.gov* not later than 30 calendar days after the date of submission'' (79 FR 69646).

Comments and Response

The comments received on the provisions specified in § 11.52 for posting of clinical trial results information pertained to the proposed quality control procedures (described in section III.C.12 of the NPRM and proposed § 11.66) and the timing of posting in relationship to those procedures. These comments are addressed in full in Section IV.D.3 of this preamble which addresses the requirements for corrections in § 11.64(b)(1) (which now includes the provisions proposed in § 11.66). We describe here the comments specific to the timeline for posting. Some commenters supported the proposal for posting, however, a number of commenters favored the quality control review of information and suggested that information on both registration and results should be posted only after quality control review process has concluded. Commenters expressed concern about the potential to misinform those using the public record and suggested only posting sections that have fulfilled quality control criteria. Some commenters suggested that the harm of posting information before the quality control review process has concluded is greater than the benefit of posting the information in a timely manner. While we understand these concerns, we interpret the statutory posting deadline to be a clearly delineated timeline between submission and posting. In addition, in the event that a study record is posted in accordance with the statutory posting deadline and the quality control review process has not concluded, the clinical trial record will contain information that will be visible to those viewing the record on *ClinicalTrials.gov* to make it clear that the quality control review process has not concluded for the posted clinical trial information.

Final Rule

Taking into consideration the commenters' concerns and the statutory requirements for posting clinical trial results information, we maintain the NPRM proposal in the final rule. For clarity, we have modified the title of § 11.52 such that it is now ''By when will the NIH Director post submitted clinical trial results information?'' As discussed further in the preamble for § 11.10, we clarified that clinical trial results information means the data elements the responsible party is required to submit to *ClinicalTrials.gov* as specified in the PHS Act or as specified in these regulations, as applicable. Thus, we have clarified § 11.52 by removing the phrase ''submitted under this subpart.'' We have also clarified that the requirement does not apply to information submitted under section 402(j)(4)(A) of the PHS Act and § 11.60.

Section 11.52 applies only to clinical trial results information required to be submitted to *ClinicalTrials.gov*. Reflecting section 402(j)(2)(C) of the PHS Act, as codified in § 11.42, clinical trial results information is required to be submitted for certain applicable clinical trials ''for which clinical trial registration information is required to be submitted'' (see § 11.42(a) and (b)). Section 11.22 specifies which applicable clinical trials must be registered. For such trials that voluntarily register with *ClinicalTrials.gov*, regardless of whether they are subject to the requirements for voluntary submission under § 11.60 or are subject to the requirements in § 11.60(a)(2)(ii), we intend to post results information as soon as practicable after clinical trial results information has been submitted and after the issues identified during quality control are corrected or adequately addressed.

6. § 11.54—What are the procedures for requesting and obtaining a waiver of the requirements for clinical trial results information submission?

Overview of Proposal

Section 402(j)(3)(H) of the PHS Act provides that ''[t]he Secretary may

waive any applicable requirements of this paragraph [(3) of the PHS Act] for an applicable clinical trial, upon written request from the responsible party, if the Secretary determines that extraordinary circumstances justify the waiver and that providing the waiver is consistent with the protection of public health or in the interest of national security . . .'' The statute also stipulates that if such a waiver is granted, the Secretary will notify the appropriate congressional committees that the waiver has been granted and explain why it has been granted, not later than 30 calendar days after the waiver has been granted. Proposed § 11.54 implemented this provision by outlining procedures by which a responsible party may submit a written request for a waiver from the requirements of subpart C for an applicable clinical trial. Proposed § 11.54(a) specified the details for the submission and content of the waiver request, including that the request identify the specific requirement(s) for which the waiver is requested. Proposed § 11.54(b) specified the procedures and deadlines for appealing a denied waiver request, and § 11.54(c) provided that the Director would include a notation in the clinical trial record for the waived results submission requirement and that the Secretary would notify the appropriate congressional committees of the waiver and why it was granted (79 FR 69646).

The proposed rule noted that we expected that waivers would be requested and granted in only a very limited number of situations, and we described an example of a situation in which a waiver might be granted, namely if results information could be submitted only in a manner that would likely enable the re-identification of clinical trial participants. We invited public comments on other situations in which a waiver might be granted and would be consistent with the protection of public health or in the interest of national security. With regard to the notation on the clinical trial record, we explained that it was intended to inform users of *ClinicalTrials.gov* that the absence of certain results information does not constitute a failure to comply with the statute and implementing regulation. We also explained that because the waiver would be based on extraordinary circumstances that could include considerations of public health and/or national security, we proposed that we would not publicly post information describing the reason for the waiver. We invited public comment on this proposal as well (79 FR 69646).

Comments and Response

Several commenters addressed the Agency's proposed procedures for handling waiver requests. Commenters suggested additional examples of situations that they thought would warrant a waiver of the results information submission requirements. Several commenters suggested that a waiver was warranted when the principal investigator could no longer serve as the responsible party such as when the investigator relocates or in the event of their death or disability. Commenters suggested that a waiver would relieve the institution of the burden of having to fulfill the responsible party's obligations to submit results information. We do not consider a principal investigator's inability to fulfill their responsibilities as an extraordinary circumstance that would satisfy the statutory standard. Section 11.4(c)(3) provides for the reassignment of the responsible party function when the principal investigator no longer meets or is no longer able to meet all of the requirements for designation as the responsible party or in the event of the principal investigator's death or incapacity. Other comments emphasized the importance of maintaining flexibility in the process of considering requests for waivers for results information reporting and asserted that without flexibility in the system, waiver requests may be unnecessarily denied. We believe that the proposed rule provides the necessary mechanisms and the flexibility for considering waivers while also protecting public health and national security.

Comments were also received suggesting that the proposed rule's 15 calendar day deadline for data submission following waiver denial or appeal denial should be extended, including a proposal to allow the waiver request to be submitted 60 calendar days before the results information submission deadline, allowing the Secretary 30 calendar days to transmit a decision and an additional 60 calendar days for an appeal resolution. We agree with the comments that longer timeframes are appropriate and have included 30-calendar day deadlines in the final rule.

Commenters also supported the use of justified waiver requests as well as a publicly posted notation on the clinical trial record if results information submission is waived. Other commenters suggested making the waiver request and appeal public and allowing the public to appeal a reason given in a waiver request by a responsible party. Since the waiver would be based on extraordinary circumstances that could include considerations of public health and/or national security, the Agency will retain the proposed approach of not posting information describing the reason for the waiver.

Final Rule

Taking into consideration the public comments and the statutory requirements set forth in section 402(j)(3)(H) of the PHS Act, the final rule retains the proposed rule with the exception of the timeframes for submitting results information after a waiver denial, for appealing a waiver denial, and for submitting results information after a denial of the waiver on appeal. These timeframes have been extended from 15 calendar days to 30 calendar days. The final rule also clarifies in § 11.54(d) that for an applicable clinical trial with a primary completion date before the effective date of the rule, the responsible party may submit a waiver request as specified in section 402(j)(3)(H) of the PHS Act. This is consistent with the differing requirements that apply to applicable clinical trials, depending on the primary completion date of the applicable clinical trial, as discussed further in Section IV.F of this preamble. Section 11.54 of the rule outlines procedures by which a responsible party may submit a request for a waiver from any or all requirements of results information submission. We expect that waivers will be requested and granted only for extraordinary circumstances that could include the need to protect the public health and/or the interests of national security. The Agency will issue guidance on how to submit such waiver requests.

Section 11.54(a) of the rule specifies that waiver requests must be submitted by the responsible party to the Secretary or a delegated official in the format specified at *https://prsinfo.clinicaltrials.gov/* (or successor site) and indicate the NCT number, Brief Title, and Name of the Sponsor of the applicable clinical trial. This information is necessary to ensure accurate identification of the specific trial for which the waiver is requested (*i.e.,* the combination of NCT number and Brief Title will assist in identifying mistyped NCT numbers) and the key parties involved (*i.e.,* sponsor and responsible party). Since the statute grants the Secretary the authority to waive ''any applicable requirements'' for the submission of results information if justified by ''extraordinary circumstances,'' the rule

requires the responsible party to identify the specific provisions(s) for which a waiver is requested and provide a description of the extraordinary circumstances that are believed to justify the waiver. The responsible party will not be required to comply with the results information submission provisions in subpart C for which the waiver is granted. Such provisions could include all or just some of the provisions for which the waiver is requested. The responsible party will continue to be required to comply with any remaining provisions of subpart C for which the waiver is not requested or not granted. It is important to note, however, that a responsible party may still need to provide certain information in the PRS to indicate that the results information submission requirement was waived for that information. After a waiver is granted, the Agency will work with the responsible party to address the specific requirements that are waived. In some cases, for example, the responsible party may need to enter ''0 participants'' with an explanation that a waiver was provided for such information. While a waiver request is pending, the responsible party will not be required to submit other required clinical trial results information. The deadline for submitting results information to *ClinicalTrials.gov* is the later of the original submission deadline or 30 calendar days after a notification denying the waiver is sent to the responsible party.

Section 11.54(b) details the process by which a responsible party may appeal a denied waiver request to the Secretary or delegated official and indicates that additional information about the format of the appeal will be specified at *https://prsinfo.clinicaltrials.gov/* (or successor site). If this responsibility is delegated to a Department or Agency official, the delegated official will, as a matter of practice, differ from the delegated official for reviewing the initial waiver request. As with the original request, the responsible party is not required to comply with specific provisions of subpart C for which the waiver is granted upon appeal. For the provisions for which a waiver is not granted upon appeal, the responsible party is required to submit results information by the later of the original results information submission deadline or 30 calendar days after the notification denying the appeal is sent to the responsible party. Of note, we have replaced the word ''transmitted,'' used in the proposed rule, with the phrase ''sent to the responsible party'' in final § 11.54(b)(1) and added the phrase ''to the responsible party'' in final § 11.54(b)(3). Although these changes do not alter the meaning of these provisions, we believe they further clarify that the responsible party has 30 calendar days from the date the notification is sent from the Agency as evidenced by the date stamp on the notification.

Section 11.54(c)(1) requires the Director to include a notation in the clinical trial record that specified elements of the results information submission requirements have been waived. This notation is intended to inform users of *ClinicalTrials.gov* that the absence of certain results information does not necessarily constitute a failure to comply with the statute and implementing regulation. Section 11.54(c)(2) implements section 402(j)(3)(H) of the PHS Act by requiring the Secretary, if a waiver is granted, to notify the appropriate congressional committees that the waiver has been granted and explain why it has been granted, not later than 30 calendar days after any part of the waiver is granted. Since the waiver would be based on extraordinary circumstances that could include considerations of public health and/or national security, the Agency will not post publicly information describing the reason for the waiver.

Section 11.54(d), as described above, states that a responsible party for an applicable clinical trial with a primary completion date before the effective date of the rule may request a waiver from any of the applicable requirement(s) for clinical trial results information submission in accordance with the procedures specified in section 402(j)(3)(H) of the PHS Act.

D. Subpart D—Additional Submissions of Clinical Trial Information

1. § 11.60—What requirements apply to the voluntary submission of clinical trial information for clinical trials of FDA-regulated drug products (including biological products) and device products?

Overview of Proposal

Proposed § 11.60 described requirements that would apply to voluntary submissions of information for certain clinical trials not otherwise subject to the registration and results information submission requirements of section 402(j) of the PHS Act. Section 402(j)(4)(A) of the PHS Act specified that ''[a] responsible party for a clinical trial that is not an applicable clinical trial, or that is an applicable clinical trial that is not subject to paragraph (2)(C), may submit complete clinical trial information described in paragraph (2) or paragraph (3) [of the PHS Act] provided the responsible party submits clinical trial information for each applicable clinical trial that is required to be submitted under section 351 [of the PHS Act] or under section 505, 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act in an application or report for licensure, approval, or clearance of the drug or device for the use studied in the clinical trial.'' Based on this provision, the proposed rule described two types of clinical trials of FDA-regulated drugs or devices for which submission of information is not otherwise required: (1) Clinical trials that do not meet the definition of an applicable clinical trial; and, (2) clinical trials that are applicable clinical trials but are not required to register under proposed section § 11.22(a) (*i.e.,* clinical trials that are applicable clinical trials that were initiated on or before September 27, 2007, and that reached their completion dates before December 26, 2007) (79 FR 69647).

Under proposed § 11.60, if a responsible party voluntarily submitted clinical trial information for either type of clinical trial for which submission of information is not otherwise required, the responsible party would be required to submit registration information as specified in proposed § 11.60(a)(2)(i)(A) or results information as specified in proposed § 11.60(a)(2)(i)(B) for the voluntarily submitted clinical trial. In addition, proposed § 11.60(a)(2)(ii) and § 11.60(a)(2)(iii) described additional applicable clinical trials (*i.e.,* ''triggered'' trials) for which clinical trial information would be required to be submitted if a responsible party voluntarily submitted clinical trial information for a clinical trial not otherwise required to be registered. In this context, ''triggered'' trials referred to ''each applicable clinical trial that is required to be submitted under section 351 [of the PHS Act] or under section 505, 510(k), 515, or 520(m) of the [FD&C] Act in an application or report for licensure, approval, or clearance of the drug or device for the use studied in the clinical trial'' as specified in section 402(j)(4)(A) of the PHS Act. Requiring the submission of information for ''triggered'' trials helps prevent selective voluntary submissions of results information from clinical trials that only show positive results for a particular product, but not from those applicable clinical trials that show negative or uncertain results for the same product (79 FR 69648). Additionally, proposed § 11.60(a)(2)(iv) provided deadlines applying to voluntary submissions and proposed § 11.60(a)(2)(v) specified that

all voluntary submissions would be subject to the update and corrections requirements proposed in §§ 11.64 and 11.66, respectively. Finally, proposed § 11.60(b) provided a statement to accompany applicable clinical trial information that was submitted voluntarily as specified in section 402(j)(3)(D)(v)(V) of the PHS Act (79 FR 69649).

Comments and Response

Several commenters addressed proposed § 11.60. Some commenters supported the proposed requirements, while one suggested that the scope of the mandatory submission requirements should be modified to encompass all trials covered by the proposed voluntary submissions requirements, including those of currently marketed drugs and devices completed before the enactment of FDAAA. The Agency appreciates these comments and the underlying sentiment for broad trial registration and results information reporting policies. We note that responsible parties have always been able to submit voluntarily the registration and/or results information for clinical trials of currently marketed drugs and devices that were completed before the enactment of FDAAA. We also note that § 11.60 of the final rule provides that, as of September 27, 2007, responsible parties who make such voluntary submissions and are manufacturers of the studied product must also submit clinical trial information for all ''triggered'' applicable clinical trials required to be provided to FDA in a marketing application or premarket notification, in order to avoid selective disclosure of information about a product on *ClinicalTrials.gov.*

Other commenters suggested that the Agency consider including fewer requirements in the final rule to encourage more voluntary submissions, while another requested the removal of proposed requirements for updating and correcting voluntarily submitted trial information because of concerns that such a burden may have the unintended consequence of discouraging voluntary submissions. In response, the Agency has reviewed proposed § 11.60(a) and determined that each requirement is necessary to ensure that voluntary submissions would be provided in accordance with the statute. Further, we have added the Study Completion Date data element, as defined in § 11.10 of the final rule and discussed in Section IV.A.5 of this preamble, to the list of required additional results data elements that must be provided when the responsible party voluntarily submits clinical trial results information for a clinical trial for which the clinical trial registration information specified in § 11.60(b)(2)(i)(B), and 11.60(c)(2)(i)(B) have not been submitted. The Study Completion Date is needed to identify that the requirements for voluntary partial results information submission in § 11.60(a)(2)(iv)(A), 11.60(b)(2)(iv)(A), and 11.60(c)(2)(iv)(A), and obligations for updates and corrections in §§ 11.60(c)(2)(v) and 11.64 have been fulfilled. That is, even though a responsible party for a trial may need to submit partial results information several times voluntarily in order to meet different deadlines (*i.e.,* because of different dates for final data collection for primary and/or secondary outcome measures or for the pre-specified time frame for collecting adverse events), that responsible party's obligation for voluntary results information submission is only completely fulfilled after all required results information is submitted not later than 1 year following the Study Completion Date. With regard to the updating and correction requirements in proposed § 11.60, section 402(j)(4)(A) of the PHS Act provides that voluntary submissions of information must consist of ''complete'' clinical trial registration and/or results information. The updating requirements help ensure that any subsequent changes in clinical trial information for a voluntarily submitted trial (*e.g.,* overall recruitment status) are reflected in the data bank. Additionally, the error correction requirements provide for the timely revision of submitted clinical trial information. As with mandatory submissions, these requirements are intended to help assure that all voluntary submissions are complete and accurate.

A commenter expressed concerns over a statement to accompany applicable clinical trials submitted voluntarily in proposed § 11.60(b). The commenter suggested that submitted statements may be written in language too technical for the public to understand and recommended several approaches to clarifying the meaning, such as providing a hyperlink to a page containing an explanation written in non-technical language or amending the statement directly with non-technical language. The Agency agrees that the proposed language was too technical and has modified the statement in the final rule by adding a non-technical first sentence and placing the original technical statement in parenthesis for clarity: ''This clinical trial information was submitted voluntarily under the applicable law and, therefore, certain submission deadlines may not apply. (That is, clinical trial information for this applicable clinical trial was submitted under section 402(j)(4)(A) of the Public Health Service Act and 42 CFR 11.60 and is not subject to the deadlines established by sections 402(j)(2) and (3) of the Public Health Service Act or 42 CFR 11.24 and 11.44.)''

In addition, a few commenters requested clarification on additional issues. In particular, one commenter requested clarification of the word ''triggered'' as used in the preamble section of the proposed rule. In the preamble of the proposed rule and this final rule, we use the term ''triggered'' to refer to the statutory requirement that a responsible party who has voluntarily submitted clinical trial information for a clinical trial that is not an applicable clinical trial or that is an applicable clinical trial that is not subject to the registration requirements, and who is the manufacturer of the FDA-regulated drug product (including a biological product) or device product being studied, must also submit clinical trial information for each applicable clinical trial required to be submitted to FDA in a marketing application or premarket notification for approval, licensure, or clearance of the drug product (including a biological product) or device product for the use studied in the voluntarily submitted trial. However, the term ''triggered'' is not used in the regulatory text of the final rule in § 11.60.

Another commenter expressed concern that proposed § 11.60 could be used for the voluntary submission of clinical trial information for studies of unproven stem cell and cell based therapy interventions to *ClinicalTrials.gov* as ''phase 1'' trials for promoting medical tourism and other activities. The comment further suggested that the Agency consider additional requirements for voluntary submissions in the final rule, such as review of the approval status for each submitted intervention by the relevant competent authorities. The Agency appreciates these comments and the underlying sentiment for trial registration and results reporting information. Nevertheless, allowing voluntary submissions for clinical trials not otherwise subject to submission requirements under section 402(j) of the PHS Act or this final rule increases public access to information about clinical trials regardless of the apparent nature, quality, or other characteristics of a clinical trial. Making the clinical research enterprise more transparent allows the public to track ongoing trials and informs decision makers involved

with clinical trial policies and practices (Section I of this preamble discusses public health benefits of registration and results reporting).

One commenter suggested that the Agency develop results templates for observational studies, which some sponsors may want to report at *ClinicalTrials.gov.* Observational studies that are not pediatric postmarket surveillances of a device are not subject to section 402(j) of the PHS Act. In the future, we may consider developing tools to assist sponsors who provide optional results information for observational studies (other than certain pediatric postmarket surveillances of a device product that are not a clinical trial), which are outside the scope of this rule. The Agency does provide online access to results templates for interventional studies to assist and guide responsible parties in submitting results information under section 402(j) of the PHS Act [Ref. 111].

Another commenter sought clarification about whether linking study results that have been published or posted on another Web site would be permitted for clinical trials that were voluntarily submitted with registration information only. *ClinicalTrials.gov* currently provides a number of optional data elements such as Citations and Links, which can be used to link a record to relevant trial results cited in publications or are available at a another Web site, respectively. These optional data elements will continue to be available on *ClinicalTrials.gov.* Note that, as discussed in greater detail in Section III.B of this preamble, such links to other studies and Web sites from *ClinicalTrials.gov* do not constitute a government affirmation or verification that the information within or referenced in the database, or communications that rely on that information, are truthful and non-misleading.

Final Rule

Taking into consideration the commenters' suggestions and the statutory requirements for voluntary submissions, the final rule retains the requirements as proposed in § 11.60(a), but modifies the statement from proposed § 11.60(b) to accompany voluntarily submitted applicable clinical trials and clarifies that ''drug'' means ''drug product'' and ''device'' means ''device product.'' In addition, consistent with the discussion in Section IV.F of this preamble, we have made revisions to address the differing requirements that apply to applicable clinical trials (and, if voluntarily submitted, other clinical trials).

Section 11.60(a) applies to clinical trials initiated before the effective date of the final rule and that have a primary completion date before the effective date of the final rule. Consistent with the discussion in Section IV.F, below, those clinical trials would be subject to the registration requirements specified in section 402(j)(2)(A)(ii) of the PHS Act and subject to results information submission requirements specified in sections 402(j)(3)(C) and 402(j)(3)(I) of the PHS Act. Section 11.60(b) applies to clinical trials initiated before the effective date of the final rule and that have a primary completion date on or after the effective date of the final rule. Consistent with the discussion in Section IV.F, below, those clinical trials would be subject to the registration requirements specified in section 402(j)(2)(A)(ii) of the PHS Act and subject to results information submission requirements specified in 42 CFR part 11. Section 11.60(c) applies to clinical trials initiated on or after the effective date of the final rule and that have a primary completion date on or after the effective date of the final rule. Consistent with the discussion in Section IV.F, below, those clinical trials would be subject to the registration and results information submission requirements specified in 42 CFR part 11.

Section 11.60(a)(1), (b)(1), and (c)(1) specify that the requirements for voluntary submission of clinical trial information apply to two types of clinical trials for which submission of information is not otherwise required, as follows: (1) Clinical trials of FDA-regulated drug products (including biological products) or device products that do not meet the definition of an applicable clinical trial (*e.g.,* a phase 1 drug trial or small feasibility device study); and, (2) clinical trials that are applicable clinical trials that were initiated on or before September 27, 2007, and that reached their completion dates before December 26, 2007 (*i.e.,* applicable clinical trials not required to be registered under section 402(j)(2)(C) of the PHS Act or § 11.22(a), as applicable). We interpret section 402(j)(4)(A) of the PHS Act in a way that is consistent with the scope of FDA's regulatory authorities and the scope of this regulation. Thus, § 11.60 applies only to clinical trials of FDA-regulated drug products (including biological products) and device products. For example, this section applies to a phase 1 trial of an FDA-regulated drug product (including a biological product) or a small clinical trial that evaluates the feasibility of an FDA-regulated device product, but does not apply to a clinical trial that studies only behavioral interventions that are not drug products (including biological products) or device products.

In addition, as explained in the proposed rule, we interpret the phrase ''applicable clinical trial that is not subject to [the mandatory registration requirement of] paragraph (2)(C),'' in section 402(j)(4)(A) of the PHS Act, to mean a clinical trial that meets the definition of an applicable clinical trial, as specified in section 402(j)(1)(A) of the PHS Act and this part, but that was initiated on or before September 27, 2007, and that reached its completion date prior to December 26, 2007 (79 FR 69647).

In considering the information that must be submitted to *ClinicalTrials.gov* for a voluntarily submitted clinical trial, we interpret section 402(j)(4)(A) of the PHS Act as permitting a responsible party to voluntarily submit registration information for a clinical trial, results information, or both. Thus, § 11.60(a)(2)(i), (b)(2)(i), and (c)(2)(i) expressly permit the voluntary submission of registration information, results information, or both. When a responsible party voluntarily submits only registration information for a clinical trial, § 11.60(a)(2)(i)(A), (b)(2)(i)(A), and (c)(2)(i)(A) establish that registration information specified in section 402(j)(2)(A)(ii) of the PHS Act or specified in § 11.28(a) (as applicable) must also be submitted.

For clinical trials with a primary completion date on or after the effective date, § 11.60(b)(2)(i)(B) and (c)(2)(i)(B) specify that when a responsible party voluntarily submits results information for a clinical trial for which registration information is specified in section 402(j)(2)(A)(ii) of the PHS Act or specified in § 11.28(a) (as applicable) has not been submitted, results information as specified in § 11.48(a), as well as additional descriptive information set forth in § 11.60(b)(2)(i)(B) and (c)(2)(i)(B) and defined in § 11.10(b), must be submitted. We believe that such additional descriptive information is necessary to enhance access to and understanding of the results of a clinical trial of a drug product (including a biological product) or device product (*e.g.,* Study Phase is necessary to enable a user to understand the relative stage of development of an experimental drug product (including a biological product) studied in a clinical trial). Further, we believe that several other data elements must be submitted with voluntarily submitted results information in order for the Agency to confirm that a clinical

trial for which information is voluntarily submitted is not an applicable clinical trial subject to mandatory registration or results information submission under this part (*e.g.,* Product Manufactured in and Exported from the U.S., and U.S. Food and Drug Administration IND or IDE Number). For situations in which a responsible party submits voluntarily only clinical trial results information under section 402(j)(4)(A) of the PHS Act, the Agency is using its authority under section 402(j)(3)(D)(iii)(IV) of the PHS Act to interpret results information to include the data elements under § 11.60(a)(2)(i)(B) and (c)(2)(i)(B) in addition to the data elements set forth in § 11.48(a). We have added § 11.60(a)(2)(i)(C), (b)(2)(i)(C), and (c)(2)(i)(C) to clarify that a responsible party who voluntarily submits registration information and voluntarily submits results information for a clinical trial must submit registration information as specified in section 402(j)(2)(A)(ii) of the PHS Act or specified in § 11.28(a) (as applicable) and results information specified in sections 402(j)(3)(C) and 402(j)(3)(I) of the PHS Act or specified in § 11.48(a) (as applicable).

Sections 11.60(a)(2)(ii), (b)(2)(ii), and (c)(2)(ii) require that a responsible party who submits clinical trial information voluntarily for a clinical trial must additionally submit clinical trial information for any applicable clinical trial (including those initiated on or before September 27, 2007, and reached their completion date prior to December 26, 2007) that is required to be submitted in a marketing application or premarket notification to FDA for approval, licensure, or clearance of the drug product (including a biological product) or device product for the use studied in the voluntarily submitted clinical trial. The final rule maintains the approach in the proposed rule by clarifying that this statutory requirement applies to (1) applications or premarket notifications submitted to the FDA by a manufacturer on or after September 27, 2007; and (2) when the responsible party for the voluntarily submitted clinical trial is also the manufacturer submitting the marketing application or premarket notification, thereby avoiding the situation in which a responsible party would be required to submit information for triggered applicable clinical trials for which they are not the responsible party and do not have access to the relevant data. While the Agency encourages submissions of registration information and results information for all types of clinical trials, regardless of whether they are subject to section 402(j) of the PHS Act, responsible parties should consider the above requirements before deciding whether to register a clinical trial or submit results information voluntarily.

In the final rule, § 11.60(a)(2)(iii), (b)(2)(iii), and (c)(2)(iii) specify that the clinical trial information required to be submitted for a triggered applicable clinical trial is, at minimum, the same as that for the voluntarily submitted clinical trial. That is, if a responsible party voluntarily submits registration information for a clinical trial pursuant to § 11.60(a), the responsible party must submit registration information specified in section 402(j)(2)(A)(ii) of the PHS Act for any triggered applicable clinical trial(s). Similarly, if a responsible party voluntarily submits clinical trial results information for a clinical trial pursuant to § 11.60(a), then the responsible party must submit results information specified in sections 402(j)(3)(C) and 402(j)(3)(I) of the PHS Act for any triggered applicable clinical trial(s). Since the submission of clinical trial information for a triggered applicable clinical trial is a condition of voluntary submission, the Agency does not propose to treat the submission of such information as a voluntary submission under § 11.60(a)(2)(ii), (b)(2)(ii), and (c)(2)(ii) that itself could trigger the submission of clinical trial information for other applicable clinical trials. In other words, the submission of information for an applicable clinical trial that is triggered under section 402(j)(4)(A) of the PHS Act and subject to § 11.60 would not, in turn, itself trigger the requirement to submit information for additional applicable clinical trials under that section. For example, voluntary submission of information for trial X may trigger the submission of information for applicable clinical trials Y and Z that were required to be included in FDA marketing application 001, as required under § 11.60(a)(2)(ii), (b)(2)(ii), and (c)(2)(ii). However, submission of information for applicable clinical trials Y and Z would not further trigger the requirement to submit information for additional applicable clinical trials (*e.g.,* even if applicable clinical trial Y were used to support marketing application 002, the applicable clinical trials required to be included in 002 would *not* be triggered).

In general, an initial voluntary submission is not subject to any regulatory deadlines in §§ 11.24 and 11.44 and so may be submitted at any time in relation to the conduct of the trial (*e.g.,* before, during, or after the study start date or primary completion date). However, when a voluntary submission is made, § 11.60(a)(2)(iv), (b)(2)(iv), and (c)(2)(iv) establish two deadlines that apply to voluntary submissions of results information. Sections 11.60(a)(2)(iv)(A), (b)(2)(iv)(A), and (c)(2)(iv)(A) specify that if data collection for the secondary outcome measure(s) or the pre-specified timeframe for collecting adverse event information for such clinical trials is not completed by the primary completion date of the voluntarily submitted clinical trial, then results information for the secondary outcome measure(s) and/or adverse event information must be submitted by the later of either the date that the results information is voluntarily submitted for the primary outcome measure(s) or 1 year after the date on which (1) the final subject was examined or received an intervention for the purposes of final collection of data for the secondary outcome measure(s) or (2) after the final subject was observed for adverse events, whether the clinical trial was concluded according to the pre-specified protocol or was terminated. We clarify that while initial voluntary submission of partial results information is permitted (pending completion of data collection for secondary outcomes and/or the pre-specified time frame for collecting adverse events information according to the reporting deadlines specified in § 11.60(a)(2)(iv)(A), (b)(2)(iv)(A), and (c)(2)(iv)(A)), the responsible party is required to submit the clinical trial results information specified in sections 402(j)(3)(C) and 402(j)(3)(I) or specified in § 11.48(a) (as applicable) that is otherwise available when submitting partial results information. This means that, with respect to adverse event information, a responsible party would be required to submit information summarizing serious and frequent adverse events recorded to-date each time results information for a secondary outcome is submitted, until all the adverse event information required by this part has been submitted. This clarification is now included in the final rule in § 11.60(a)(2)(iv)(A)(*2*), (b)(2)(iv)(A)(*2*), and (c)(2)(iv)(A)(*2*). We emphasize, however, this provision does not impose requirements on the design or conduct of the clinical trial or on the data that must be collected during the clinical trial.

Sections 11.60(a)(2)(iv)(B), (b)(2)(iv)(B), and (c)(2)(iv)(B) specify that clinical trial information for triggered applicable clinical trials must be submitted not later than the date on which the application or premarket notification is submitted to FDA or the

date on which clinical trial information is submitted for the voluntarily submitted clinical trial to *ClinicalTrials.gov,* whichever is later. This approach prevents a responsible party from having to submit information for a clinical trial that is not subsequently included in the marketing application or premarket notification. Section 11.60(c)(2)(v) specifies that responsible parties who voluntarily submit clinical trial information to *ClinicalTrials.gov* would be required to update and correct submitted information, including information submitted for triggered trials, in accordance with § 11.64 (as applicable).

Section 11.60(d) specifies the text of the statement to accompany voluntarily submitted applicable clinical trials to clarify that the voluntary submission was not subject to the deadlines imposed by section 402(j) of the PHS Act for mandatory submission of registration and results information. The required statement would apply to any applicable clinical trial, including any triggered applicable clinical trial, submitted under section 402(j)(4)(A) of the PHS Act and § 11.60(a), (b), and (c). Accordingly, the statement will be as follows: ''This clinical trial information was submitted voluntarily under the applicable law and, therefore, certain submission deadlines may not apply. (That is, clinical trial information for this applicable clinical trial was submitted under section 402(j)(4)(A) of the Public Health Service Act and 42 CFR 11.60 and is not subject to the deadlines established by sections 402(j)(2) and (3) of the Public Health Service Act or 42 CFR 11.24 and 11.44.)''

2. § 11.62—What requirements apply to applicable clinical trials for which submission of clinical trial information has been determined by the Director to be necessary to protect the public health?

Overview of Proposal

The NPRM, in accordance with section 402(j)(4)(B) of the PHS Act, proposed in § 11.62 to require submission of clinical trial information if the Director determines that the posting of such information on *ClinicalTrials.gov* is necessary to protect the public health. Section 402(j)(4)(B)(i) of the PHS Act specifically authorizes the Secretary to ''require by notification'' of the submission of clinical trial information ''in any case in which the Secretary determines for a specific clinical trial [. . . .] that posting in the registry and results data bank of clinical trial information for such clinical trial is necessary to protect the public health.'' This authority has been delegated to the Director (74 FR 19973, Apr. 30, 2009). If the Director so determines, clinical trial information must be submitted for that clinical trial in accordance with sections 402(j)(2) and (3) of the PHS Act, except with regard to timing requirements. With respect to timing, such clinical trial information must be submitted to *ClinicalTrials.gov* ''not later than 30 days after the date specified by the [Director] in the notification,'' unless the responsible party submits a certification for delayed results information submission under section 402(j)(3)(E)(iii) of the PHS Act (see section 402(j)(4)(B)(i)(II) of the PHS Act).

The NPRM proposed in § 11.62(a) to implement this provision by requiring the responsible party for an applicable clinical trial who receives notification pursuant to section 402(j)(4)(B) of the PHS Act that the Director has determined that posting of clinical trial information is necessary to protect the public health to submit such information to *ClinicalTrials.gov* in accordance with proposed § 11.62(c) (79 FR 69650).

The NPRM proposed in § 11.62(b) to implement section 402(j)(4)(B)(ii) of the PHS Act, which specifies that the types of clinical trials subject to this provision are limited to those that are: (1) ''an applicable clinical trial for a drug that is approved under section 505 of the Federal Food, Drug, and Cosmetic Act or licensed under section 351 of [the PHS Act] or for a device that is cleared under section 510(k) of the Federal Food, Drug, and Cosmetic Act or approved under section 515 or section 520(m) of [the FD&C Act], whose completion date is on or after the date 10 years before the date of the enactment of the Food and Drug Administration Amendments Act of 2007'' (*i.e.,* September 27, 1997) or (2) an applicable clinical trial that is subject to registration under section 402(j)(2)(C) of the PHS Act and studies a drug or device that is unapproved, unlicensed, or uncleared regardless of whether or not approval, licensure, or clearance was sought as described in section 402(j)(3)(D)(ii)(II) of the PHS Act (79 FR 69650).

Section 11.62(c) of the NPRM specified that such clinical trial information must be submitted to *ClinicalTrials.gov* not later than 30 calendar days after the date specified by the Director in the notification, unless the responsible party submits a certification for delayed results submission, as specified in § 11.44(b) or (c). It further proposed that if the responsible party submitted clinical trial registration information prior to the date on which the notification is sent to the responsible party, the responsible party must then make all necessary updates, if any, to the submitted information not later than 30 calendar days after the date specified in the notification (79 FR 69650). The Agency invited public comment on the types of situations in which the posting of clinical trial information might be necessary to protect the public health and on the criteria that the Director should consider when making such a determination, but no comments were received on the types of trials that should be included.

Comments and Response

One commenter addressed proposed § 11.62. The comment suggested that the Agency should describe the criteria to be used by the Director to determine when applicable clinical trials subject to § 11.62 would be required to submit clinical trial information to *ClinicalTrials.gov.* The Agency will issue guidance at a later date on factors that the Director intends to consider in determining whether clinical trial information subject to § 11.62 must be posted on *ClinicalTrials.gov.* We expect this authority to be rarely invoked and limited to extraordinary circumstances including those in the interest of public health or in the interest of national security.

Final Rule

Taking into consideration the commenter's suggestion and the statutory requirements for applicable clinical trials for which submission of clinical trial information has been determined by the Director to be necessary to protect the public health, the final rule maintains the proposed § 11.62 approach, except we clarify that ''drug'' means ''drug product'' and ''device'' means ''device product'' in final § 11.62(b)(1) and 11.62(b)(2). We also clarify in final § 11.62(b)(2) that the applicable clinical trial is subject to this section ''regardless of whether approval, licensure, or clearance was, is, or will be sought, and that is not otherwise subject to results information submission in accordance with the regulation.'' As explained in the discussion of § 11.10 of this preamble (Section IV.A.5), approval status of a product studied in an applicable clinical trial (*i.e.,* either ''unapproved, unlicensed, or uncleared'' or ''approved, licensed, or cleared'') is interpreted to be the approval status of the product on the primary completion date. In this context, the approval status

of the product is the approval status on the estimated or actual primary completion date on the date that the Director notifies the responsible party that clinical trial information must be submitted to *ClinicalTrials.gov* for an applicable clinical trial under § 11.62.

The clinical trials specified in § 11.62(b)(1) would consist of applicable clinical trials of approved, licensed, or cleared drugs (including biological products) or devices that reached their primary completion dates on or after September 27, 1997. We note that this set of clinical trials would include applicable clinical trials that reach their primary completion dates on or after the date of enactment of FDAAA, many of which already would be subject to the registration and results information submission requirements of section 402(j) of the PHS Act, with the exception of applicable clinical trials that were initiated prior to the date of enactment of FDAAA (*i.e.,* September 27, 2007) and were not ongoing as of December 26, 2007.

The clinical trials specified in § 11.62(b)(2) would consist of applicable clinical trials that are required to register at *ClinicalTrials.gov* pursuant to § 11.22(a) of this rule and that study drugs (including biological products) or devices that are unapproved, unlicensed, or uncleared by the FDA (regardless of whether or not approval, licensure, or clearance was sought). This set of clinical trials would consist of registered applicable clinical trials that would not otherwise be required to submit clinical trial results information to *ClinicalTrials.gov*.

Section 11.62(c) specifies which information must be submitted to *ClinicalTrials.gov* and the timelines for submitting such information. In general, we interpret the references to ''clinical trial information'' and submission ''in accordance with paragraphs (2) and (3)'' in section 402(j)(4)(B)(i)(I) of the PHS act to mean registration information and results information as required in §§ 11.28(a) and 11.48(a), respectively. Consistent with section 402(j)(4)(B)(i)(II) of the PHS Act, such information must generally be submitted not later than 30 calendar days after the date specified by the Director in the notification. We note that section 402(j)(4)(B)(i)(II) of the PHS Act permits an exception to the submission deadline for results information if a responsible party submits a certification for delayed results information submission not later than 30 days after the submission date specified by the Director in the notification. We also note that if the responsible party has submitted such a certification under § 11.44(b) or (c), only the submission of results information will be delayed. Accordingly, if a responsible party for an unregistered applicable clinical trial subject to § 11.62 submits a certification not later than 30 calendar days after the submission date specified in the Director's notification, the responsible party still would be required to submit registration information not later than 30 calendar days after the submission date specified in the notification, although results information would be required to be submitted by the applicable deadline established under § 11.44(b) or (c).

To clarify the submission requirement in situations in which registration information was submitted to *ClinicalTrials.gov* before a notification was sent to the responsible party, § 11.62(c)(3) indicates that the registration information must be updated, if necessary, not later than 30 calendar days after the submission date specified in the notification. Notwithstanding this initial update, the requirements of § 11.64 would apply to clinical trial information submitted pursuant to § 11.62.

All clinical trial information submitted to *ClinicalTrials.gov* under § 11.62 will be subject to the quality control procedures described in § 11.64(b)(1). The Agency intends to post such information as soon as practicable after it has completed the quality control review process. The timeline for posting would apply to all clinical trial information submitted under § 11.62, including registration information for an applicable clinical trial of a device that has not previously been approved or cleared by the FDA. Section 402(j)(4)(B) of the PHS Act applies equally to applicable clinical trials of drugs and devices that are approved, licensed, or cleared or are unapproved, unlicensed, or uncleared. It applies to ''any case'' in which the Director, as delegated by the Secretary, determines that posting of clinical trial information on *ClinicalTrials.gov* (not just submission of the information to *ClinicalTrials.gov*) is necessary to protect public health. Although section 402(j)(4)(B) of the PHS Act specifically allows for a delay in submission of results information if the responsible party submits a certification for delayed results information submission under section 402(j)(3)(E)(iii) of the PHS Act, it does not specifically delay or prohibit posting submitted registration information until a device is cleared or approved. Therefore, the Agency believes that registration information for all applicable clinical trials under § 11.62 may be posted after quality control review has concluded, regardless of the approval, licensure, or clearance status of the device products studied. Of note, we do not interpret section 402(j)(4)(B) of the PHS Act to permit a responsible party to request a waiver of the requirement to submit clinical trial information pursuant to a notification from the Director under § 11.62. The language of section 402(j)(4)(B) of the PHS Act states ''Notwithstanding paragraphs (2) and (3)'' (note that waivers are in paragraph (3)), and only makes the exception for trials with a certification for delayed results information submission, as described above. Therefore, it does not make an exception for trials for which a waiver was granted.

3. § 11.64—When must clinical trial information submitted to *ClinicalTrials.gov* be updated or corrected?

Proposed §§ 11.64 and 11.66, which described the requirements and procedures for clinical trial information updates and corrections respectively, are combined in the final rule under the new § 11.64—*When must clinical trial information submitted to ClinicalTrials.gov be updated or corrected?,* described herein.

Overview of Proposal

When must clinical trial information submitted to *ClinicalTrials.gov* be updated?

Section 402(j)(3)(D)(v)(IV) of the PHS Act provides that the regulations shall also establish ''the appropriate timing and requirements for updates of clinical trial information, and whether and, if so, how such updates should be tracked.'' Section 402(j)(4)(C) of the PHS Act separately requires responsible parties to submit updates of clinical trial registration information to *ClinicalTrials.gov* not less than once every 12 months (except for certain specified data elements for which more rapid updates are required) and the Director to post such updates publicly in the data bank. With regard to the requirement in section 402(j)(3)(D)(v)(IV) of the PHS Act to establish, by regulation, ''the appropriate timing and requirements for updates of clinical trial information . . .,'' we noted in the NPRM that we interpret the term ''clinical trial information'' to mean both clinical trial registration information and clinical trial results information, consistent with the definition of ''clinical trial information'' in section 402(j)(1)(A)(iv) of the PHS Act. In addition, our proposed requirements for updates

apply to adverse event information because adverse event information is deemed to be clinical trial results information under section 402(j)(3)(I)(v) of the PHS Act (79 FR 69587).

Proposed § 11.64(a)(1) established a general requirement for responsible parties to update clinical trial information not less than once every 12 months if there are changes to any of the data elements previously submitted. Section 11.64(a)(2) emphasized that this requirement to update clinical trial information not less than once every 12 months includes a requirement to update the estimated Primary Completion Date data element, unless there have been no changes in the preceding 12 months. We noted that, in our view, the public should be able to rely upon the accuracy of this date to assist them in determining when results information may be available on *ClinicalTrials.gov*. In general, we recommended that the complete clinical trial record on *ClinicalTrials.gov* be reviewed not less than once every 12 months to help ensure that the clinical trial information it contains remains accurate. Proposed § 11.64(a)(3) specified that updates to clinical trial information must be submitted until the date on which all required clinical trial results information has been submitted to *ClinicalTrials.gov,* meaning results for all primary and secondary outcome measures and all adverse events collected in accordance with the protocol. After that time, the proposed rule stated, submitted clinical trial information would continue to be subject to the corrections provisions in proposed § 11.66 of the NPRM, and responsible parties would be required to submit corrected information when the responsible party or the NIH becomes aware of any errors or needed corrections in the clinical trial information (79 FR 69651).

Proposed § 11.64(b) identified data elements that must be updated not later than 30 calendar days after a change occurs, including those already specified in section 402(j)(4)(C)(i) of the PHS Act (*i.e.,* Recruitment Status and Clinical Trial Completion Status). Additional data elements identified for more frequent updates were: Study Start Date; Intervention Name(s); Availability of Expanded Access; Expanded Access Status; Overall Recruitment Status and, if the status changes to suspended, terminated, withdrawn, an explanation about why the study was stopped; and if the status change is terminated or active, not recruiting, the actual enrollment data; Individual Site Status; Human Subjects Protection Review Board Status; Completion Date; Responsible Party, by Official Title; and Responsible Party Contact Information. Furthermore, § 11.64(b) proposed an even more frequent update timeline of not later than 15 calendar days for updating the U.S. FDA Approval, Licensure, or Clearance data element, and stated that the Record Verification Date must be updated any time the responsible party reviews the complete record for accuracy, even if no other updates are submitted at that time (79 FR 69653). It also specified that if a protocol is amended in such a manner that changes are communicated to participants in the clinical trial, updates to relevant clinical trial information must be submitted no later than 30 calendar days after the protocol amendment is approved by the human subjects protection review board (79 FR 69587).

We noted that the above exceptions to the 12-month period for updates are considered important for patients using the data bank to search for clinical trials for which they might qualify and for the Agency in administering other provisions of section 402(j) of the PHS Act. In addition, proposed § 11.64(c) would require a responsible party to update, as necessary, any previously submitted clinical trial information at the time results information is submitted to *ClinicalTrials.gov* (the responsible party would then be required to update the Record Verification Date data element). The NPRM suggested that doing so will improve the accuracy of information that is used by *ClinicalTrials.gov* to automatically prepopulate some elements of results information. As set forth in proposed § 11.64(d)(2), submitted clinical trial information that is posted in accordance with §§ 11.35 and 11.52, including past updates of posted submissions, are tracked in the *ClinicalTrials.gov* archive, in which the history of changes to clinical trial information for any clinical trial is accessible to the public (79 FR 69587).

What are the requirements for corrections of clinical trial information?

Proposed § 11.66 of the NPRM set out requirements for responsible parties to correct clinical trial information submitted to *ClinicalTrials.gov*. This included clinical trial information voluntarily submitted under section 402(j)(4)(A) of the PHS Act and/or proposed § 11.60, as well as clinical trial information necessary to protect the public health and submitted under section 402(j)(4)(B) of the PHS Act and/or proposed § 11.62. Proposed § 11.66 addressed several types of corrections (*i.e.* correction of errors, correction of falsified data and other corrections). The discussion in the NPRM preamble regarding § 11.66 indicated that some errors and other deficiencies are expected to be detected during quality review procedures conducted by the Director (79 FR 69654). Section 402(j)(3)(D)(v)(III) of the PHS Act states that regulations shall establish ''procedures for quality control . . . with respect to completeness and content of clinical trial information under this subsection, to help ensure that data elements are not false or misleading and are non-promotional.'' The discussion of ''Quality Control Procedures'' in Section III.C.12 of the NPRM outlined the quality control process that would occur with clinical trial information as part of submission. This included a two-step process by which an automated system-based check would occur prior to submission followed by a detailed, manual review after submission. This detailed review would be based on quality review criteria for identifying apparent errors, deficiencies, or inconsistencies that are not detected by the automated checks. If any such problems are identified in the detailed, manual review, the proposed rule stated, the Director would send an electronic notification to the responsible party, indicating that the submission contains apparent errors, deficiencies, and/or inconsistencies listing such issues and requesting correction. Consistent with proposed § 11.66 on correction of errors, the NPRM further outlined that responsible parties would be required to correct the errors, deficiencies, and/or inconsistencies in clinical trial information not later than 15 calendar days after being informed of them by the Agency (or otherwise becoming aware of them), whichever is later. The NPRM also recognized that because clinical trial information will have to be posted not later than the 30 day posting deadlines specified in §§ 11.35 and 11.52, there may be some situations in which submitted clinical trial information is posted before it has been corrected. We noted that it would be necessary to include information indicating that such information has not completed the quality control process as well as implementing other mechanisms to help users of *ClinicalTrials.gov* identify such clinical trial records (79 FR 69586).

Although the statute did not establish timelines for correcting errors, § 11.66 proposed that corrections needed to be submitted after the responsible party becomes aware that submitted clinical trial information is incorrect or falsified or that corrections are needed for other

reasons. Section 11.66(a) required responsible parties to correct errors not later than 15 calendar days after the error is discovered. Section 11.66(b) covered falsified data and proposed to require notification to the Director of the falsification and submission of corrected information not later than 15 calendar days after the corrected information becomes available or notification not later than 15 calendar days after determining that the information cannot be corrected or is correct. Section 11.66(c) addressed ''other corrections of clinical trial information'' which were identified as ''various other deficiencies'' including but not limited to ''inconsistencies in submitted data, for example, a mismatch between the reported number of subjects enrolled in a clinical trial and the sum of reported number of subjects assigned to different arms . . .''(79 FR 69655) and stated that a responsible party who becomes aware or is informed by NIH that such corrections are needed must make them as soon as possible but not later than 15 calendar days after becoming aware or being informed of the problem.

Comments and Response

When must clinical trial information submitted to *ClinicalTrials.gov* be updated?

Commenters addressed the update provisions in § 11.64, with some in support of the proposed approach, while others suggested changes to the required updates and the proposed timelines. Among those who suggested changes, commenters suggested that the specific timelines for updates were too short. Some commenters suggested alternative timelines for updates, including that the general timeline for updates should be extended from not less than once every 12 months to once every 18 months; the 30-day timeframe for rapid updates should be extended to 45 or 60 days; and that all the timelines for each rapid update element should be consistent (*i.e.,* the timeline for updating the U.S. FDA Approval, Licensure, or Clearance data element should also be 30 calendar days). Although commenters suggested extending the timelines, the 12 month general timeline is established by section 402(j)(4)(C)(i)(I) of the PHS Act. Similarly, the 30 day timeline following changes to Overall Recruitment Status and Completion Date is established by section 402(j)(4)(C)(i)(III) and section 402(j)(4)(C)(i)(IV) of the PHS Act. While the statute would allow for modifying the 30 day timeline for other data elements, sufficient evidence of burden was not provided by the public comments indicating that these deadlines would be difficult to meet. Moreover, we believe it makes sense, in the interest of simplicity (as has also been sought by commenters), to keep the timeline for updates consistent to the extent possible. Finally, rapid updating of this information is consistent with the stated purpose of *ClinicalTrials.gov* set forth in section 402(j)(2)(A)(i) of the PHS Act to ''enhance patient enrollment and provide a mechanism to track subsequent progress of clinical trials.'' If such key changes were not reflected in the record in *ClinicalTrials.gov* for as long as 12 months after the change, then the Agency believes that the value of *ClinicalTrials.gov* as a source of reliable, accurate information for the public and potential participants in clinical trials would be compromised.

Commenters also raised issues regarding specific data element update requirements. One disagreed with the requirement that actual enrollment data be provided when the Overall Recruitment Status changes (*i.e.,* trial's recruitment status changes to ''terminated'' or ''active, not recruiting'') and suggested that the NIH continue to allow submission of actual enrollment data at the time of overall study completion (*e.g.,* LPLV). The Agency believes that submission of actual enrollment information at the time that recruitment is no longer occurring (Overall Recruitment Status is ''terminated'' or ''active, not recruiting'') would permit users of *ClinicalTrials.gov* to know more quickly whether the clinical trial achieved its target enrollment. However, we also recognize the potential burden and some of the challenges with providing such information in a more rapid manner. In the final rule, therefore, we modify the requirement to be consistent with current practice at *ClinicalTrials.gov* by requiring actual enrollment to instead be updated within 30 calendar days of reaching the Primary Completion Date.

Another commenter opposed the requirement that the status of individual sites be updated because of concerns about burden on large international trials. The Agency believes that changes in recruitment status should be communicated promptly so that potential human subjects can know whether or not a clinical trial is currently recruiting subjects. In addition, prompt updates to Overall Recruitment Status as well as Individual Site Status support the purpose of *ClinicalTrials.gov* to enhance patient enrollment by assisting potential human subjects who search for clinical trials by location and wish to retrieve information about only those trials that are open to recruitment in specified locations. We clarify that when the Overall Recruitment Status is other than ''recruiting,'' the Individual Site Status no longer needs to be updated because a change in the Overall Recruitment Status would apply to each individual site and the Individual Site Status will no longer be displayed by *ClinicalTrials.gov* on the publicly posted study record. We also note that the update burden to responsible parties is reduced by tools available in the PRS that allow for easily changing the Individual Site Status (*e.g.,* from ''recruiting'' to ''active, not recruiting'') for many sites at once.

Another commenter raised a question about which IRB approval date is relevant in a multi-site trial involving multiple IRBs in response to the requirement to update the record not later than 30 calendar days after an amended protocol is approved by an IRB that involves changes that are communicated to participants. We clarify that the date of the first IRB approval for the amendment should be used. We note that we invited public comment on other thresholds (other than those changes that are communicated to enrolled participants) that could be used to determine which protocol changes are significant enough to warrant 30-day updating of affected clinical trial information, but none was received.

Comments were also raised in opposition to the proposal to require voluntarily registered trials to comply with the update and correction timelines due to the burden involved. It was suggested that the requirement may have the unintended consequence of decreasing voluntary submissions and, thereby, transparency. The Agency believes that in order to maintain the value of *ClinicalTrials.gov* as a source of accurate and up-to-date clinical trial information each record, including voluntary submissions, must be updated in accordance with the timelines outlined in the final rule. Other commenters requested that a mechanism be included in the PRS to make clear to responsible parties when they have fulfilled all obligations to update the study record, and no further updates are required. Proposed § 11.64(a)(3) indicated that the responsible party must continue to submit updates until complete ''clinical trial results information specified in § 11.48 has been submitted for all primary and secondary outcomes and all adverse events that were collected in accordance with the protocol.'' We agree with the commenters on the need for

being able to identify when the obligation to update and/or correct clinical trial information has ended. As one component of this determination, we have added to §§ 11.10(a) and 11.28, the Study Completion Date data element to identify ''the date the final subject was examined or received an intervention for purposes of final collection of data for the primary and secondary outcome measures and adverse events (*e.g.,* last subject's last visit) . . .'' Providing the Study Completion Date as clinical trial information and including it as a data element that must be updated within 30 calendar days of a change is consistent with the stated purpose of *ClinicalTrials.gov* to ''. . . provide a mechanism to track subsequent progress of clinical trials'' (see section 402(j)(2)(A) of the PHS Act). Further, it establishes the date on which the final subject was examined (or received an intervention) for purposes of final data collection, thereby identifying the maximum date under § 11.44(d) by which partial results information must be submitted (*i.e.,* no later than one year after the Study Completion Date).

The NPRM indicated that the obligation to update ends after submission of complete clinical trial results information. We clarify that the obligation to submit updates ends after all required clinical trial results information has been submitted as specified in sections 402(j)(3)(C) and 402(j)(3)(I) of the PHS Act or as specified in § 11.48, as applicable, and after any corrections have been made or addressed as required under § 11.64(b). We note that one reason it is important for the update requirements to continue through the conclusion of the quality control process is to ensure that the Responsible Party and Responsible Party Contact Information remains accurate during that process. We also have clarified that for any clinical trials that are not subject to the clinical trial results information submission requirements, the obligation to update ends on the date on which all required clinical trial registration information has been submitted as specified in section 402(j)(2)(A)(ii) of the PHS Act or § 11.28, as applicable, and corrections have been made or addressed in response to any electronic notice received under § 11.64(b)(1).

What are the requirements for corrections of clinical trial information?

Commenters addressing the proposed quality control procedures and/or the corrections provisions proposed in § 11.66 commented on the amount of time a responsible party has to correct clinical trial information, timing of posting of clinical trial information in relationship to quality control procedures, and the falsified data provisions. Each of these topics is discussed in turn.

Commenters submitting input on the corrections provisions in § 11.66 of the NPRM expressed general support for the requirement to correct errors and some commenters also supported the 15 day timeline for addressing corrections. Other commenters expressed concern about the timeline for correction of errors, as they found it too short and suggested that it was insufficient, unrealistic, and burdensome. Commenters suggested that a rush by responsible parties to meet the deadline might result in the unanticipated submission of more errors. Alternative timeframes were proposed by commenters, who suggested extending the correction of error timeline to 30 days, 45 days, and 60 days. One commenter proposed allowing 15 days for the responsible party to notify the NIH from the time an error is discovered followed by a 30 day timeline to make any corrections. As noted in the NPRM discussion of quality control procedures (Section III.C.12), the Agency expects to conduct a quality control review and also aims to receive submission of corrected clinical trial information prior to the deadlines for posting such information publicly as specified in §§ 11.35 and 11.52 (*i.e.,* not later than 30 calendar days after submission). We are, therefore, maintaining the proposed timeline of 15 calendar days for the responsible party to correct clinical trial registration information after a notification is sent by the Director, but we are extending the timeline for correction of clinical trial results information to ''25 calendar days.'' These timelines are in place for two reasons: (1) To allow, in some cases, corrected clinical trial information to be submitted by the responsible party in a timeline that would allow for quality control review and posting in accordance with the timelines in §§ 11.35 or 11.52; and, (2) to minimize the amount of time that posted clinical trial information is available without conclusion of the quality control review process. In our experience in operating the registry component of *ClinicalTrials.gov,* we have found that clinical trial registration information can be reviewed quickly and that responsible parties can submit corrected information, if necessary, in a matter of days. However, allowing for a longer timeline for corrections of clinical trial results information acknowledges the inherent difference in complexity of the information as compared to clinical trial registration. To better distinguish between corrections that may be needed based on quality control by the Director and other corrections that are needed based on identification by the responsible party, we are modifying the corrections provisions in the final rule to address these separately. When a responsible party becomes aware of errors, the timelines to correct or address such errors are 15 calendar days for registration information and 25 calendar days for results information. We clarify in the discussion of the final rule requirements for corrections, the steps that can be taken when the Director notifies a responsible party of issues.

As initially discussed in the context of §§ 11.35 and 11.52, a number of commenters expressed the importance of quality control and suggested that both registration and results information should be posted only when quality control review criteria have been fulfilled. Commenters expressed concern about the potential to misinform those using the publicly posted study record and suggested only posting sections that have fulfilled quality control criteria. Some commenters suggested that the harm of posting information that has not passed quality control review is greater than posting the information in a timely manner. While we understand these concerns, section 402(j)(3)(G) of the PHS Act established for applicable clinical trials that the Director of NIH is required to post results information ''publicly in the registry and results database not later than 30 days after such submission.'' In addition, because there may be cases in which clinical trial information is posted without conclusion of the quality control review process, a shorter timeline for corrections will minimize the amount of time such records are posted. In the event that a study record is posted in accordance with the statutory posting deadline, and the quality control review has not concluded, the clinical trial record will contain information that will be visible to the public explaining that the quality control review process for the posted clinical trial information has not concluded.

Regarding the proposed statements on a study record, commenters were concerned that users of *ClinicalTrials.gov* may not understand such notices and may make decisions based on information that is inaccurate, unclear, or incomplete. To address this concern, we will evaluate whether there are ways in which the notices for each

record could specify the data element(s) identified by the Agency that may contain errors, deficiencies, and/or inconsistencies, and aim to employ other measures to ensure that the notice is clear and limited to the relevant sections. We note that the quality control review process will continue even after the information is posted with a notice indicating the process has not concluded. The general quality control review process and the specific criteria utilized by the Director to evaluate submitted results will be available at *https://prsinfo.clinicaltrials.gov* (or successor site), prior to the effective date, for responsible parties and the public to have a better understanding of the types of issues reviewed.

Responsible parties must correct or address apparent errors, deficiencies, and/or inconsistencies within 15 calendar days (clinical trial registration information) or 25 calendar days (clinical trial results information) of the date the Director provides electronic notification to the responsible party. Quality control review procedures will be followed for any subsequent submission of revised clinical trial information. When the responsible party submits revised clinical trial information, or provides explanatory information that addresses the apparent errors, deficiencies, and/or inconsistencies, any revised information will be posted after quality control review. Further, when all apparent errors, deficiencies, and/or inconsistencies have been addressed, the statement that the quality control review process had not concluded will be removed from the posted record. However, the clinical trial information that was initially posted will appear in the archived history for that clinical trial record, and the archived version will indicate that it had been posted with a notice. The electronic notification sent to the responsible party indicating that the quality control review process has concluded will inform responsible parties of these facts. We hope this notification further encourages those with posted records that contain such a statement to correct the information or address the issues raised by the quality control review process as soon as possible, to help ensure that users of *ClinicalTrials.gov* may rely on the information in the trial records, as intended.

Some commenters requested more information, such as additional guidance regarding quality control processes, while others made suggestions, such as NIH development of common standards for quality control or development of a process that involves domain experts. To assist responsible parties in avoiding such errors, deficiencies, and inconsistencies prior to this final rule, we developed and continued to refine documentation explaining how to meet the quality review criteria; identified and compiled lists of frequent errors, deficiencies, and inconsistencies in submitted results information; and, provided system support to help responsible parties minimize such errors, deficiencies, and inconsistencies. We also have provided intensive user support for responsible parties who are new to the online submission process, particularly for results information, whether through data entry using Web-based forms or automated uploading of data files. In particular, we provide one-on-one assistance to support a responsible party in submitting their clinical trial results information. We have developed and posted draft educational materials, such as tips on improving results information submissions and ways to avoid common errors, deficiencies, and inconsistencies observed in submissions to date. All such documents are available at *https://prsinfo.clinicaltrials.gov* (or successor site). We will continue to provide such support to responsible parties and, based on these interactions, develop new or updated materials in order to facilitate and streamline preparation of clinical trial information for submission to *ClinicalTrials.gov* and to help ensure that the submissions meet the quality review criteria.

Commenters also addressed the falsified data correction provision proposed in § 11.66(b) and suggested that it was vague and unclear about when errors should be reported as falsified data and how responsible parties are to determine when sufficient credible evidence exists to warrant a falsification report. They noted that no guidelines were provided for what events should trigger a presumption that data may be false and what constitutes a suitable investigation, and no distinctions were made about materiality, *e.g.,* inaccuracies about the recruitment status versus inaccuracies about the validity of safety data. Commenters inquired about the sanctions that would go with each determination (error versus falsification) and asserted that a more clearly defined and formal process would need to be in place to ensure a thorough investigation is conducted before inaccuracies are reported as falsified data. In addition, commenters suggested that the falsification provision could result in depriving responsible parties of their right to due process under the Fifth Amendment because it would require companies to report falsification without establishing clear parameters for what constitutes falsification. One commenter asserted that, given that there are criminal penalties for making false statements to the Government, the offense must be sufficiently explicit to inform those who are bound by the law of the specific conduct that will subject them to criminal penalties. A commenter suggested that it was inappropriate to incorporate into the NPRM a definition of falsification from FDA's proposed Reporting Information Regarding Falsification of Data regulation (Docket No. FDA–2008–N–0115, 75 FR 7412 (Feb. 19, 2010)). Commenters also suggested that the certification and falsification provisions should undergo a separate rulemaking process to determine what constitutes falsification and intent, and such process should be used and carried out in conjunction with FDA and other federal biomedical research stakeholders to propose a system for addressing the important and complicated issues related to intentional research falsification. Another commenter suggested that a disclaimer should be included in clinical trial records to inform the public that *ClinicalTrials.gov* is not responsible for the accuracy of the study results. Based on consideration of these comments, the final rule eliminates the distinctions between the types of errors (*i.e.* errors, falsifications, other errors) and simplifies the regulatory approach for correction of errors as described below and in § 11.64(b). From a database integrity standpoint, the distinction between an inadvertent and a deliberate error is not material, and eliminating this distinction is responsive to concerns raised by public comments. However, we emphasize existing mechanisms that address scientific misconduct (see § 11.6 and Section IV.A.3 of this preamble).

Final Rule

Taking into consideration commenters' suggestions regarding both updates (proposed § 11.64) and corrections (proposed § 11.66), as well as the statutory requirements, the final rule combines these sections into the new § 11.64—*When must clinical trial information submitted to ClinicalTrials.gov be updated or corrected?* While both the updates and corrections provisions in these sections include specific timelines by which clinical trial information must be updated or corrected, we encourage responsible parties to update or correct

information as soon as possible to help the ensure that posted clinical trial information is accurate and up-to-date for those that rely on the information on *ClinicalTrials.gov*. Additionally, final § 11.64(a) clarifies that ''drug'' means ''drug product.''

Required updates are described in § 11.64(a), which generally retains the NPRM proposal for required updates but modifies the requirement for the timing of updating actual enrollment information. Consistent with the revisions discussed in preceding sections of this preamble, § 11.64(a) also adds a requirement to update Study Completion Date and clarifies the requirements for data elements related to expanded access. In addition, we clarify how a responsible party indicates that there were no changes to clinical trial information in the previous 12 month period. Modifications were also made to clarify when a responsible party's obligation to update and correct clinical trial information ends. In addition, consistent with the discussion in section IV.F of this preamble, we made revisions to address the differing requirements that apply to applicable clinical trials (and, if voluntarily submitted, other clinical trials).

For clinical trials initiated before the effective date of the final rule, § 11.64(a)(1)(i)(A) establishes a general requirement for responsible parties to update clinical trial registration information specified in section 402(j)(2)(A)(ii) not less than once every 12 months if there are changes to any of the data elements previously submitted. Section 11.64(a)(1)(i)(B) and (a)(1)(i)(C) detail the requirement to update the Overall Recruitment Status data element not later than 30 calendar days after any change in overall recruitment status and the Primary Completion Date data element not later than 30 calendar days after the clinical trial reaches its actual primary completion date.

For clinical trials initiated on or after the effective date of the final rule, § 11.64(a)(1)(ii)(A) establishes a general requirement for responsible parties to update clinical trial registration information specified in § 11.28 not less than once every 12 months if there are changes to any of the data elements previously submitted. Section 11.64(a)(1)(ii)(B) through (a)(1)(ii)(O) establish requirements for a responsible party to update certain clinical trial registration information more rapidly after a change in the status or conduct of a clinical trial or pediatric postmarket surveillance of a device product. The NIH recognizes that it would be impractical and potentially burdensome to responsible parties to require rapid updates to all clinical trial information data elements each time a change occurs, but we believe that changes to certain data elements beyond those required to be rapidly updated in section 402(j) of the PHS Act are sufficiently time-sensitive to require updates more rapidly than once every 12 months.

Section 11.64(a)(1)(ii) outlines the requirements for updating the following 14 data elements:

(1) *Study Start Date.* The Study Start Date data element must be updated from estimated to actual not later than 30 calendar days after the first human subject is enrolled in the clinical trial. This requirement applies to clinical trials for which an estimated study start date is provided at the time of registration, rather than an actual study start date, *i.e.,* clinical trial registration information was submitted prior to enrollment of the first human subject. The update ensures that potential human subjects know in a timely fashion that recruitment has begun. It also ensures that the record reflects the actual start date, as opposed to an estimated start date, and it provides a mechanism to demonstrate whether a clinical trial has been registered not later than 21 calendar days after enrollment of the first subject.

(2) *Intervention Name(s).* The Intervention Name(s) data element must be updated to a non-proprietary name not later than 30 calendar days after a non-proprietary name is established for an intervention studied in a clinical trial. Intervention Name is frequently used as a search term to identify and retrieve clinical trials of interest. If it is not updated for as long as a year, users of *ClinicalTrials.gov* will not be able to accurately retrieve trials of interest during that time or to easily compare information among multiple trials of the same intervention.

(3) *Availability of Expanded Access.* Clinical trial information submitted under the Availability of Expanded Access data element in § 11.28(a)(2)(ii)(H) must be updated by the responsible party who is both the manufacturer of the drug and the sponsor of the applicable clinical trial not later than 30 calendar days after expanded access becomes available. Similarly, the data element must be updated not later than 30 calendar days after the date on which the responsible party receives an NCT number for the expanded access record. This data element informs patients whether access to an investigational drug product (including a biological product) to treat serious or life-threatening diseases or conditions is available outside of the applicable clinical trial. Expanded access may not be available at the time clinical trial registration information is submitted, and expanded access may no longer be available on a date other than the primary completion date of the applicable clinical trial. Therefore, there are specific update requirements:

First, when expanded access for a particular investigational drug product (including a biological product) becomes available after registration information has been submitted for applicable clinical trial(s) of that investigational product, if the responsible party for the applicable clinical trial(s) is both the manufacturer of the investigational product and the sponsor of the applicable clinical trial, the responsible party must update the Availability of Expanded Access data element in § 11.28(a)(2)(ii)(H) not later than 30 calendar days after expanded access becomes available.

Second, not later than 30 calendar days after expanded access becomes available, if the responsible party is both the manufacturer of the investigational drug product and the sponsor of the applicable clinical trial, the responsible party must create an expanded access record by submitting the data elements required under § 11.28(c), unless an expanded access record for the investigational drug product has already been created. The responsible party is required to enter the NCT number of the expanded access record in the relevant clinical trial record(s) not later than 30 calendar days after the date on which the responsible party receives such NCT number. We note that we have removed the NPRM proposal to also require a responsible party to update the Availability of Expanded Access data element not later than 30 calendar days after termination of the expanded access program. The provision of the NCT number of the expanded access record as well as the requirement to update the Expanded Access Record data element as described in § 11.64(a)(1)(ii)(E) will allow for *ClinicalTrials.gov* to ensure that information on the availability of expanded access is accurately displayed on the relevant posted record(s), while reducing the update burden on a responsible party.

We note that, as discussed below, § 11.64(a)(3) establishes when a responsible party's obligation to submit updates for clinical trial information ends. Even if an investigational product has not been approved or licensed at the time the updating requirement ends, we strongly encourage responsible parties to continue to update the Expanded Access Record until the product is approved or licensed or expanded

access is no longer available. Updating this information will provide patients with accurate and up-to-date information about the availability of investigational products, which we believe will facilitate access to such products. Second, updating expanded access records may reduce the burdens on responsible parties who are both the manufacturer and the sponsor of the applicable clinical trial, because patients who are interested in expanded access will be able to rely on the information in *ClinicalTrials.gov*, rather than having to contact the responsible party in order to obtain this information.

(4) *Expanded Access Record.* The Expanded Access Status data element in § 11.28(c)(2)(iv) must be updated not later than 30 calendar days after a change in the status of the availability of expanded access, to indicate whether access to the investigational drug product is currently available. This data element plays a role in providing information about expanded access that is similar to the role of Overall Recruitment Status in applicable clinical trials, indicating whether expanded access is currently available to patients. Expanded Access Type in § 11.28(c)(1)(x) must be updated not later than 30 calendar days after a change in the type of expanded access that is available to patients. The timely update of these data elements is important to have reflected in the data bank and is consistent with statutory requirements.

(5) *Overall Recruitment Status.* This data element must be updated not later than 30 calendar days after a change in the overall recruitment status of the clinical trial. Changes in recruitment status should be communicated promptly so that potential human subjects can know whether or not a clinical trial is currently recruiting subjects. In addition, if Overall Recruitment Status is updated to ''suspended,'' ''terminated,'' or ''withdrawn,'' the responsible party must at the same time provide information for the Why Study Stopped data element. Suspension, termination, and withdrawal of a clinical trial are significant changes that should be communicated promptly to prospective human subjects, along with the reason for the change. The responsible party will be allowed to enter this information as free-text so that he or she has flexibility to explain the reason(s) why a clinical trial stopped prematurely.

(6) *Individual Site Status.* This data element must be updated not later than 30 calendar days after a change in status for any individual site. It also supports the purpose of *ClinicalTrials.gov* to enhance patient enrollment by assisting potential human subjects who search for clinical trials by location and wish to retrieve information about only those trials that are open to recruitment in specified locations.

(7) *Human Subjects Protection Review Board Status.* This data element must be updated not later than 30 calendar days after a change in Human Subjects Protection Review Board Status. Because such information is intended to demonstrate to potential human subjects whether a registered applicable clinical trial or other clinical trial has undergone necessary human subjects protection review board review, has received necessary approvals for human subjects research, or was exempt from such review, it must be updated in a timely fashion.

(8) *Primary Completion Date.* This data element must be updated not later than 30 calendar days after a clinical trial reaches its actual primary completion date. In addition, at the time the date is changed to ''actual,'' the responsible party must also update the Enrollment data element to actual and specify the actual number of participants enrolled.

(9) *Study Completion Date.* This data element must be updated not later than 30 calendar days after a clinical trial reaches its actual study completion date.

(10) *Responsible Party, by Official Title.* This data element must be updated not later than 30 calendar days after a change in either the name of the responsible party or in the responsible party's official title. This update is necessary to enable NIH and other users of the data bank to accurately identify the responsible party for the clinical trial.

(11) *Responsible Party Contact Information.* Consistent with updates required to the Responsible Party data element, the Responsible Party Contact Information must be updated not later than 30 calendar days after a change in the responsible party or the responsible party's contact information. Given that the responsible party must make updates to clinical trial information and, in general, must submit clinical trial results information, it is essential for the Agency to know of changes to the responsible party and to responsible party contact information in a timely manner. Up-to-date information about the responsible party ensures that the Agency has contact information for the appropriate person responsible for submitting clinical trial information about the applicable clinical trial or clinical trial.

(12) *Device Product Not Approved or Cleared by U.S. FDA.* This data element must be updated not later than 15 calendar days after a change in the approval or clearance status of one or more device products studied in the applicable clinical trial. A change in the approval or clearance status of a device product can trigger a requirement for the Agency to post previously-submitted clinical trial registration information within 30 calendar days of the change in status as further discussed in Section IV.B.5 of this preamble. The 15 day deadline is a procedural necessity to provide the Agency timely notice that it must post publicly clinical trial registration information within 30 calendar days of the change in status, as required by law.

(13) *Record Verification Date.* This data element must be updated any time the responsible party reviews the complete set of submitted clinical trial information for accuracy, even if no other updated information is submitted at that time. The record verification date is intended to demonstrate when the information in *ClinicalTrials.gov* for a particular clinical trial was last checked for accuracy. As noted in § 11.28, the responsible party will be required to update the Record Verification Date if he or she examines the complete set of submitted clinical trial information (*e.g.,* as part of a monthly or annual review), even if he or she determines that no additional or updated information needs to be submitted. Similarly, the responsible party will be required to update the Record Verification Date data element if he or she updates a data element and reviews the rest of the record for accuracy. However, the responsible party is not required to update the Record Verification date if he or she submits updates to one or more data elements without reviewing the accuracy of the rest of the record. We clarify that the Record Verification Date must be updated not less than once every 12 months, even if no other updated information is submitted at that time. This approach does not require a responsible party to review records more frequently or regularly than will be needed in order to update submitted information as otherwise required by § 11.64(a), but it does require that the Record Verification Date be updated if the complete record were reviewed for accuracy during such an update and not less than once every 12 months. Doing so indicates to users of *ClinicalTrials.gov* the currency of the information and provides an additional assurance that it is up-to-date.

(14) Subsection 11.64(a)(1)(ii)(O) details that relevant clinical trial

registration information be updated not later than 30 calendar days after a protocol amendment is approved by a human subjects protection review board, if the protocol is amended in such a manner that changes are communicated to participants in the applicable clinical trial or other clinical trial.

In addition, § 11.64(a)(1)(iii) requires that responsible parties update clinical trial registration information at the time they submit clinical trial results information to *ClinicalTrials.gov* (unless there are no changes to the clinical trial registration information). If the clinical trial was initiated before the effective date of the final rule, updates to clinical trial registration information must be submitted as described in § 11.64(a)(1)(i). If the clinical trial was initiated on or after the effective date of the final rule, updates must be submitted in accordance with § 11.64(a)(1)(ii). As discussed further in Section IV.F, this approach is consistent with the Agency's interpretation of the differing requirements that apply to applicable clinical trials initiated before the effective date of the final rule and those initiated on or after the effective date of the final rule. This requirement is intended to help ensure the consistency and accuracy of information in the registry and results portions of the data bank. Updated registration information will be used to pre-populate certain data elements in the clinical trial record so that responsible parties do not have to enter them again. Because the submission and subsequent posting of clinical trial results information is often a reason for users to retrieve the record for a particular clinical trial, the additional update requirement will also ensure that users have access to complete registration and results information that is up-to-date.

For clinical trials that have a primary completion date on or after the effective date of the final rule, § 11.64(a)(2)(i) establishes a general requirement for responsible parties to update clinical trial results information not less than once every 12 months if there are changes to any of the data elements previously submitted. The final rule also clarifies that the protocol and statistical analysis plan specified in § 11.48(a)(5) and certain agreements specified in § 11.48(a)(6)(ii) are excluded from this general requirement as any changes to this content will be submitted as partial results information in § 11.44(d)(3). Section 11.64(a)(2)(ii) requires for applicable device clinical trials of unapproved or uncleared device products that the following data elements, as the data elements are defined in § 11.10(b), be updated not later than 30 calendar days after the relevant changes have occurred: Intervention Name(s), Primary Completion Date, Study Completion Date, and Overall Recruitment Status. The Record Verification Date must be updated any time the responsible party reviews the complete set of submitted clinical trial information for accuracy and not less than every 12 months. As described in Section IV.C.4 of this preamble for § 11.48(a)(7), we interpret the statute to provide the Secretary the authority to require, through rulemaking, for applicable device clinical trials of unapproved or uncleared device products this additional descriptive information that is similar to the type of information required to be submitted under section 402(j)(2)(A)(ii) of the PHS Act.

Section 11.64(a)(3) specifies that updates to clinical trial information must be submitted until the date on which all required clinical trial results information has been submitted as specified in sections 402(j)(3)(C) and 402(j)(3)(I) of the PHS Act or § 11.48 (as applicable), and all corrections have been made or addressed in response to any electronic notice received under § 11.64(b)(1). Until that point in time, submitted clinical trial information will continue to be subject to the corrections provisions in § 11.64(b), and responsible parties will be required to submit corrected information when the responsible party becomes aware of any errors in the clinical trial information. We have clarified that if no clinical trial results information is required to be submitted, a responsible party's obligation to submit updates ends on the date on which all required clinical trial registration information has been submitted as specified in section 402(j)(2)(A)(ii) of the Public Health Service Act or § 11.28, as applicable, and corrections have been made in response to any electronic notice received under § 11.64(b)(1).

We note that the updating requirements under § 11.64(a) are prompted by changes in the clinical trial and not by changes in the format in which data must be submitted to *ClinicalTrials.gov*. For example, if the Agency were to make administrative changes to the format in which clinical trial information is submitted to *ClinicalTrials.gov* after the responsible party had submitted clinical trial information as required, the Agency's revisions to *ClinicalTrials.gov* would not themselves give rise to a requirement that the responsible party update the previously submitted applicable clinical trial information. For example, if the Agency added additional options to a drop-down menu for a particular data element, even if one of the additional options is more appropriate with respect to an applicable clinical trial, the responsible party would not be required to update its previously-submitted clinical trial information, although the responsible party it could choose to do so on an optional basis. However, if a responsible party makes a required update to previously submitted clinical trial information, for example, to reflect a change in the conduct or progress of a clinical trial, the responsible party is required to submit the updated information in the format required by *ClinicalTrials.gov* at the time the update is submitted. For example, if the set of options in a drop-down menu had changed since the information had previously been submitted, the responsible party is required to select from the new set of options. We also note that if such options were modified, we would provide prior notice and seek public comment as described in Section IV.A.4, as needed.

Updates to clinical trial registration information and clinical trial results information will be posted in accordance with §§ 11.35 and 11.52, respectively. Previously posted clinical trial information will remain publicly available through the *ClinicalTrials.gov* archive. The availability of updates is codified in § 11.64(a)(4).

With regard to the requirements for corrections of clinical trial information, the final rule eliminates the distinction between the three types of corrections described in the NPRM: Errors, falsified data, and other corrections. We clarify, however, that the elimination of ''falsification'' as a type of error does not reflect a lack of concern about data integrity or tolerance by the Agency for falsification of information, and we emphasize the existing mechanisms that address scientific misconduct and falsifying information submitted to the Government in § 11.6. Instead, § 11.64(b) of the final rule requires a responsible party to correct or address (1) apparent errors, deficiencies, and/or inconsistencies identified by the Director during quality control review of submitted clinical trial information; and, (2) errors in previously submitted information identified by the responsible party. We also reiterate the procedures for quality control review that were originally described in the NPRM in Section III.C.12 and that are directly related to the corrections provisions of this final rule. Overall, we consider corrections of information to be different from updates to

information, as described in § 11.64(a). While updates are modifications to clinical trial information that reflect changes in the status or conduct of a clinical trial or the associated analysis, corrections are used to revise submitted clinical trial information that contains errors or appears to be invalid, incorrect, inconsistent, or incomplete. Because problems in clinical trial information that is (or will soon be) posted publicly need to be addressed in a timely manner in order to ensure that accurate information is available to the public, the final rule requires responsible parties to correct or address all such problems not later than 15 calendar days for clinical trial registration information and 25 calendar days for clinical trial results information after electronic notification is sent by the Director or are otherwise identified by the responsible party. A responsible party must then either correct and resubmit the clinical trial information to *ClinicalTrials.gov* or address each identified issue, such as replying by electronic notification to the Director explaining why the information is correct as submitted or why such information cannot be corrected.

Section 11.64(b)(1) specifies the requirements for correcting apparent errors, deficiencies, and/or inconsistencies identified based on quality control review procedures established by the Director (materials explaining how to meet the quality review criteria are available at *https://prsinfo.clinicaltrials.gov* or successor site). Our quality control review process is intended to help ensure that clinical trial information posted on *ClinicalTrials.gov* has facial validity and is free from obvious errors. Examples of errors, deficiencies, and/or inconsistencies that may be identified during the quality control review process include, but are not limited to, inadvertent, typographical errors, such as transpositions of numbers or characters; inadvertent omissions of data, such as omission of one component of set of participant exclusion criteria; inconsistencies in submitted data, for example, a mismatch between the reported number of subjects enrolled in a clinical trial and the sum of reported number of subjects assigned to different arms; and, incomplete entries that are insufficient to convey their intended meaning, such as a description of an outcome measure that does not describe the measurement scale being used. They also include submitted values that are demonstrably wrong, such as a mean age of participants of 624 years.

At the time of submission of clinical trial registration information, clinical trial results information, and any related updates or changes, the Agency will conduct quality control review procedures that are similar to the procedures in place before the final rule and will not affect the statutory deadlines for the submission and updating of clinical trial information (as specified in §§ 11.24, 11.44, and 11.64(a)) or publicly posting submitted clinical trial information (as specified in §§ 11.35 and 11.52). In general, we aim to complete the quality control review process and to receive submissions of corrected clinical trial information prior to the statutory deadlines for posting submitted clinical trial information publicly. We recognize that in some situations, the quality control review process may not be concluded prior to the statutory posting deadlines, and the Agency will post submitted information that may need to be corrected. Clinical trial information posted without having concluded the quality control review process, including any necessary corrections by the responsible party, will include a statement indicating that the quality control review process has not concluded. In addition, as also mentioned in Section IV.B.5 of this preamble, if the quality control review process has not concluded but the clinical trial registration information is posted to the *ClinicalTrials.gov* Web site based on the statutory posting deadline, an NCT number will not be assigned until the quality control review process has concluded. We believe additional precautions must be taken with such clinical trial registration information because it is used by the public, including by patients and healthcare providers who are considering enrollment in a clinical trial. This approach is generally consistent with the practice that has been in effect since *ClinicalTrials.gov* was launched in 2000. This approach helps ensure that the existence of an NCT number for a specific clinical trial remains an indicator both that a publicly posted clinical trial has been registered and that the clinical trial information has gone through the quality control review process. Use of NCT numbers is required in certain submissions to FDA and in reports to NIH and other HHS agencies from relevant grantees and contractors as evidence that clinical trials have been publicly registered, as required by section 402(j) of the PHS Act, and by other stakeholders, including journal editors, as evidence of public disclosure of certain protocol information. Users searching *ClinicalTrials.gov* will be able to elect to include or exclude posted study records containing clinical trial information that has not concluded the quality control review process. In addition, because the quality control review process cannot ensure the veracity of the data submitted, all entries in *ClinicalTrials.gov* will carry a disclaimer to that effect.

The quality control review process will continue even after submitted information is posted, with a notice that the quality control review process has not concluded. Specifically, responsible parties must correct or address apparent errors, deficiencies, and/or inconsistencies within 15 calendar days (clinical trial registration information) or 25 calendar days (clinical trial results information) of notification sent by the Director. For example, if quality control review identifies two or more data elements within a clinical trial record that are internally inconsistent, the responsible party will be notified that submitted clinical trial information does not appear to meet specified quality review criteria, including the identity of the particular elements involved. When the responsible party submits revised clinical trial information or provides explanatory information that addresses the apparent errors, deficiencies, and/or inconsistencies, any revised information will be posted after the quality control review. Further, when all apparent errors, deficiencies, and/or inconsistencies have been addressed, the statement that the quality control review process for that clinical trial record has not concluded will be removed from the posted record. However, the information that was initially posted will appear in the archived history for that clinical trial entry, and the archived version would indicate that it had been posted with a notice. The electronic notification sent to the responsible party would inform responsible parties of these facts.

We further explain that the quality control review process consists of two sequential components as follows: (1) An automated system-based check followed by (2) a manual review. In the first component, the *ClinicalTrials.gov* system alerts responsible parties to machine-detectable errors in the data entered (*e.g.,* certain types of missing information that is required, certain types of impossible values, certain types of internally inconsistent data). The number of automated checks the system performs has increased over time as we have gained experience with the types of errors that occur and devised additional automated rules for detection. We will continue to refine the

automated checks in order to assist submitters in detecting and minimizing errors, deficiencies, and inconsistencies in the information they are submitting. Following resolution of any errors identified by the automated system prior to submission, *ClinicalTrials.gov* staff then manually reviews data submissions to identify, based on detailed quality control review criteria, additional apparent errors, deficiencies, and/or inconsistencies not detected by the automated checks. As noted previously, if problems are identified during the manual review, an electronic notification will be sent to the responsible party, indicating that the submission contains apparent errors, deficiencies, and/or inconsistencies with a listing of the specific issues that were identified with a request for correction within 15 calendar days (clinical trial registration information) or 25 calendar days (clinical trial results information).

In the proposed rule, we detailed the steps taken to satisfy the pilot quality control project under section 402(j)(5)(C)(i) of the PHS Act that directed HHS to develop a process to help ensure that clinical trial results information submitted to *ClinicalTrials.gov* is non-promotional and is not false or misleading. The quality control study consisted of two parts as follows: (1) Review of the results of more than 4,500 clinical trials submitted under section 402(j)(3)(C) of the PHS Act after September 27, 2008; and (2) an initial validation study of the *ClinicalTrials.gov* results data bank with trial results reported in the published literature, conducted under contract by researchers at the Oregon Health Science University [Ref. 13].

Since publication of the NPRM, we have completed a third part of the QC pilot study: A validation study of the *ClinicalTrials.gov* results data bank with trial results reported in FDA review documents that are publicly available on the *Drugs@FDA* Web site, conducted under contract by researchers at The Dartmouth Institute for Health Policy and Clinical Practice [Ref. 111a]. The study determined that primary outcome descriptions for sampled trials with results available in both sources were generally consistent. However, other information could not be directly compared (*e.g.,* adverse events are reported per trial at *ClinicalTrials.gov*, but are sometimes aggregated across multiple trials on *Drugs@FDA* to summarize the overall adverse event profile of a particular product).

Given the limitations of, and differences in, the databases identified in this study and the findings from the other parts of the quality control study, we have determined that comparisons with external sources of information could not be used to validate results information submissions. Our experience reviewing submissions to date leads us to conclude that the most appropriate approach for implementing quality control procedures at *ClinicalTrials.gov* is to have all submissions undergo the two-stage quality control review process developed during the pilot study. This quality control review process focuses on the content within a study record and includes automated validation rules followed by a detailed, manual review of submitted information.

The quality control review process is conducted to help identify ''apparent errors, deficiencies, and/or inconsistencies'' in the submitted information. That process, however, cannot ensure that the submitted information is truthful and non-misleading. Therefore, compliance with the quality control review process, including the requirements set forth in § 11.64, does not constitute a legal defense to enforcement pursuant to section 301(jj) of the FD&C Act (21 U.S.C. 331(jj)), section 303(f)(3) of the FD&C Act (21 U.S.C. 333(f)(3)), or any other Federal law. A provision has been added to § 11.64 of the final rule to clarify this point.

Section 11.64(b)(2) specifies the requirements for correcting errors identified by a responsible party. It is anticipated that responsible parties may become aware of needed corrections through their own reviews of submitted data or from other parties. We, therefore, define procedures similar to those in § 11.64(b)(1) for correcting or addressing such errors, including specifying the general timeline for corrections as not later than 15 calendar days (clinical trial registration information) or 25 calendar days (clinical trial results information) after the responsible party becomes aware of any such errors. In addition, for errors that are determined by the responsible party and the Director to be uncorrectable, information will be posted on the record regarding the uncorrectable information. As specified in § 11.64(b)(2)(ii), a responsible party's obligation to submit correction of errors will end on the date on which complete clinical trial results information has been submitted as specified in section 402(j)(3)(C) and 402(j)(3)(I) of the PHS Act or § 11.48, as applicable, and corrections have been made, or addressed, in response to any electronic notice received under § 11.64(b)(1). We also have clarified that for any clinical trials that are not subject to the clinical trial results information submission requirements, the obligation to correct errors ends on the date on which complete clinical trial registration information has been submitted as specified in section 402(j)(2)(A)(ii) of the PHS Act or § 11.28, as applicable, and corrections have been made in response to any electronic notice received under § 11.64(b)(1).

E. Subpart E—Potential Legal Consequences of Non-Compliance

1. § 11.66—What are potential legal consequences of not complying with the requirements of this part?

Overview of Proposal

Other than the requirement that a responsible party not submit false or misleading information and the associated notice of potential liabilities for doing so (see § 11.6), the proposed codified text did not describe the potential legal consequences of failing to comply with the requirements of the rule. Although we did include in the preamble to the proposed rule a general discussion of the statutory procedures and penalties related to non-compliance (79 FR 69570), we did not otherwise discuss in detail the legal ramifications of failure to comply with the requirements of section 402(j) of the PHS Act, including these regulations.

Comments and Response

As discussed in Section III.A above, we received a number of comments about enforcement of the rule. Within the context of the FDAAA Title VIII statutory enforcement provisions, commenters proposed that NIH and FDA take certain approaches to enforcing the section 402(j) requirements. Commenters proposed specific penalty structures, such as only penalizing the responsible party and not the institution and making all intentional violations criminal with mandatory prison sentences. They also proposed incentives, such as providing easier submission mechanisms and citable credit for shared data sets. As previously stated, the specifics of how and under what circumstances the agencies will seek to enforce section 402(j), including the requirements of this final rule, are beyond the scope of this rulemaking. We expect that the clarification of responsibilities and obligations in this final rule will lead to a high level of voluntary compliance with these requirements. However, we believe that it also is important that responsible parties be more fully aware of the procedures and penalties to which non-compliance could subject them. Therefore, although the

procedures and penalties for non-compliance would be applicable regardless of whether they are included in the codified text, we have decided to add new § 11.66, which describes the potential legal consequences set forth in the FDAAA Title VIII enforcement provisions.

Final Rule

The final rule includes new Subpart E—Potential Legal Consequences of Non-compliance and *§ 11.66—What are potential legal consequences of not complying with the requirements of this part?* This new section describes potential civil or criminal actions, civil monetary penalty actions, and grant funding actions that may be taken because of responsible parties' failure to comply with Part 11. Not all potential legal consequences are included. For example, as discussed in relation to § 11.6, other federal laws also govern the veracity of information submitted to the Federal Government, such as 18 U.S.C. 1001 (making it a crime to make certain false statements to the executive, legislative, or judicial branch of the U.S. government). Accordingly, new § 11.66 should not be understood as describing the exclusive means of enforcement that the Government might undertake with respect to compliance with FDAAA Title VIII, including these regulations.

New § 11.66(a) describes certain non-compliant activities that can lead to civil or criminal judicial actions against the responsible parties. FDAAA Title VIII amended the FD&C Act by adding a new subsection 301(jj) (21 U.S.C. 331(jj)) to the prohibited acts provisions. New § 11.66(a)(1) describes that, under 301(jj)(1) of the FD&C Act, failure to submit the certification required by section 402(j)(5)(B) of the PHS Act, or knowingly submitting a false certification under that section, is a prohibited act. Section 402(j)(5)(B) requires submissions of new drug applications under section 505 of the FD&C Act, premarket approval applications under section 515 or 520(m) of the FD&C Act, biologics license applications under section 351 of the PHS Act, or reports under section 510(k) of the FD&C Act to be accompanied by a certification that all applicable requirements of section 402(j) of the PHS Act have been met. The applicable requirements of section 402(j) now include the requirements in Part 11.

New § 11.66(a)(2) describes that failure to submit clinical trial information required under section 402(j) of the PHS Act is a prohibited act under section 301(jj)(2) of the FD&C Act. The clinical trial information required to be submitted under Part 11 is clinical trial information required under section 402(j).

New § 11.66(a)(3) describes that submission of clinical trial information under section 402(j) that is false or misleading is a prohibited act under section 301(jj)(3) of the FD&C Act. Section 11.6 specifically provides that information submitted by a responsible party under this part ''shall not be false or misleading in any particular.'' This language in § 11.6 reflects the precise language of section 402(j)(5)(D) of the PHS Act, which is then incorporated by reference in section 301(jj)(3) of the FD&C Act's prohibited act section. Violating § 11.6 would thus be a prohibited act under section 301(jj)(3).

Judicial remedies for violations of section 301 of the FD&C Act include injunctions and criminal penalties. Under section 302 of the FD&C Act (21 U.S.C. 332), U.S. district courts have jurisdiction to restrain violations of section 301. Under section 303 of the FD&C Act persons who violate section 301 can be imprisoned or fined. Pursuant to 18 U.S.C. 3571, current generally applicable fines are (1) for individuals, up to $100,000 for a misdemeanor, up to $250,000 for a felony violation and (2) for organizations, up to $200,000 for a misdemeanor, up to $500,000 for a felony violation. Such remedies could be accomplished through judicial proceedings initiated by FDA and brought to court by the Department of Justice.

New section 11.66(b) describes generally that any person who violates section 301(jj) of the FD&C Act is subject to civil monetary penalties under section 303(f)(3) of the FD&C Act (21 U.S.C. 333(f)(3)). Under FDAAA Title VIII's addition of 303(f)(3) to the FD&C Act, a person who commits any of the prohibited acts described in section 301(jj)(1),(2), or (3) would be subject to a civil monetary penalty of ''not more than $10,000 for all violations adjudicated in a single proceeding'' (21 U.S.C. 333(f)(3)(A)). Under 402(j)(5)(C)(ii), if the Secretary determines that any clinical trial information was not submitted as required, or was false or misleading, the Secretary shall notify the responsible party and give them an opportunity to remedy the non-compliance within 30 days. As part of the civil monetary penalties provision, if the violation is not corrected within 30 days following such notification, the person is subject to an additional civil monetary penalty of ''not more than $10,000 for each day of the violation'' until the violation is corrected (21 U.S.C. 333(f)(3)(B)). With respect to the dollar amounts for the civil monetary penalties, separate laws provide for periodically adjusting for inflation the maximum civil monetary penalty amounts (the Federal Civil Penalties Inflation Adjustment Act of 1990 (28 U.S.C. 2461 note 2(a)), as amended by the Federal Civil Penalties Inflation Adjustment Act Improvements Act of 2015 (section 701 of Public Law 114–74)). FDA's procedures for administrative imposition of civil monetary penalties are in 21 CFR part 17.

New § 11.66(c) describes the FDAAA Title VIII provisions related to grant funding. Under section 402(j)(5)(A) of the PHS Act, if an applicable clinical trial is funded in whole or part by HHS, any required grant or progress report forms must include a certification that the responsible party has made all required registration and results submissions. If it is not verified that the required registration and results clinical trial information has been submitted for each applicable clinical trial for which a grantee is the responsible party, any remaining funding for a grant or funding for a future grant to such grantee will not be released. If the head of an HHS agency verifies that a grantee has not submitted such clinical trial information, the agency head will provide notice to the grantee of the non-compliance and allow the grantee 30 days to correct the non-compliance and submit the required clinical trial information. As with other matters, the head of the agency may delegate this authority to other agency officials. Registration and results information submissions required under Part 11 are required submissions for purposes of these grant funding provisions.

Although not included in § 11.66, there is a statutory provision that directs NIH to include notices in the registry and results data bank containing certain non-compliance information. Under section 402(j)(5)(E), these notices, including specified statements, alert the public to: Instances of failure to submit required information; submission of false or misleading information; penalties imposed, if any; whether the information has been corrected in the data bank; and, failure to register the primary and secondary outcomes.

F. Effective Date, Compliance Date, and Applicability of Requirements in This Part

Overview of Proposal

Section 402(j) of the PHS Act does not establish time periods for the effective date or compliance date of the rule, or the length of time between them. In the

NPRM, the effective date was 45 calendar days after the date on which the final rule is published (79 FR 69592). As of that date, the *ClinicalTrials.gov* system would be modified to allow responsible parties to comply with the rule. We further proposed that the compliance date would be 90 calendar days after the effective date (79 FR 69592), meaning that a responsible party would have until the compliance date of the rule to come into compliance with the requirements of the rule.

For applicable clinical trials, the NPRM also described in Section III.D how clinical trial records at the time of the effective date would be handled. For registration information, for information submitted on or after the effective date, the information would need to comply with the rule. For a trial ongoing as of the effective date, with registration information submitted before the effective date, the NPRM stated that the information would have to comply with § 11.28 of the rule by the compliance date. Under this proposal, responsible parties would have been required to revise and/or add registration information to comply with the rule. For an applicable clinical trial that reached its completion date prior to the effective date, the responsible party would not have been required to comply with the rule, but would have been expected to have provided registration information as required by section 402(j)(2)(A)(ii) of the PHS Act. The responsible party would also have been required to update any information necessary, consistent with section 402(j)(4)(C) of the PHS Act.

With respect to results information, section 402(j)(3)(D)(iv)(II) requires the Secretary to determine in rulemaking whether certain clinical trial information (*i.e.,* technical and non-technical summaries, full protocols, and other categories, as appropriate) ''should be required to be submitted for an applicable clinical trial for which the clinical trial information described in subparagraph (C) [basic results] is submitted to the registry and results data bank before the effective date of the regulations . . .'' The NPRM provided that the responsible parties for applicable clinical trials for which results information was submitted under section 402(j)(3)(C) of the PHS Act before the effective date would not be required to provide the results information specified in proposed § 11.48 of the rule. For an applicable clinical trial that reached its completion date prior to the effective date of the final rule, the proposal would have required the responsible party to submit all of the results information specified in proposed § 11.48 if the responsible party had not submitted results information under section 402(j)(3)(C) of the PHS Act prior to the effective date of the rule. For an applicable clinical trial with a completion date before the effective date and for which partial results were submitted prior to the effective date, but the remaining partial results were neither due nor submitted until on or after the effective date, the proposal would have required the responsible party to submit clinical trial results information under proposed § 11.48 for all outcome measures, including modifying the primary outcome measure(s) submitted before the effective date to be in accordance with the requirements specified in proposed § 11.48 (79 FR 69593). For applicable clinical trials completed before the effective date of products that are never approved, licensed, or cleared, results information would not have been required to be submitted. For applicable clinical trials completed before the effective date of unapproved, unlicensed, or cleared products that are subsequently approved, licensed, or cleared after the effective date, it was proposed that results information would be due by the earlier of 1 year after completion of the trial or 30 calendar days after FDA approval, licensure, or clearance of the studied drug or device (79 FR 69594).

The NPRM addressed how voluntary submissions under § 11.60 (for applicable clinical trials for which registration clinical trial information were not required to be submitted or clinical trials of FDA-regulated drugs or devices that are not applicable clinical trials) would be handled at the time of the effective date. It was proposed that voluntary submissions made on or after the effective date must comply with the final rule, regardless of trial completion date (79 FR 69594).

The NPRM also addressed how updates and corrections to submitted clinical trial information (§§ 11.64 and 11.66) would be handled:

- For clinical trial registration or clinical trial results information due on or after the effective date, the responsible party would be required to comply with proposed § 11.64 for updating the information.
- For clinical trial information due prior to the effective date, the responsible party would be required only to update the information in accordance with section 402(j)(4)(C) of the PHS Act.
- For an applicable clinical trial that reaches its completion date prior to the effective date, but for which results information are due after the effective date, the responsible party would be required to update *registration* information according to section 402(j)(2)(A)(ii) of the PHS Act, but update *results* information (submitted after the effective date) according to proposed § 11.64.
- For an applicable clinical trial that is registered in accordance with section 402(j)(2) of the PHS Act but is ongoing as of the effective date, because the responsible party would be required to submit registration information consistent with proposed § 11.28 by the compliance date, updates would also be required according to proposed § 11.64.

The NPRM also stated that if the responsible party is aware of clinical trial information that contains errors, the responsible party would be required to submit corrections according to § 11.66, regardless of when that information was originally submitted (79 FR 69594).

Comments and Response

Commenters expressed opinions on a variety of points related to the proposed effective and compliance dates of the rule. Regarding the timeline, commenters suggested an effective date later than the proposed 45 calendar days after the rule's publication, such as 90 calendar days after the rule's publication. Similarly, commenters suggested an compliance date later than the proposed 90 calendar days after the effective date, such as 180 calendar days after the effective date. Others supported a phased implementation of the rule's requirements to permit increased institutional readiness and to allow HHS to address practical compliance barriers that might arise during the early stages of the rule's implementation, including the updating of *ClinicalTrials.gov* to accommodate clinical trial information from new types of trials.

First, we have extended the effective date from 45 calendar days to provide at least 120 calendar days after filing for public inspection of this rule by the Office of the Federal Register. However, but the compliance date will remain 90 calendar days after the effective date. This extended effective date will allow responsible parties subject to the rule more time to review the new requirements and prepare, update, and reconfigure their institutional operations and databases appropriately. It will also allow *ClinicalTrials.gov* additional time to ensure system readiness by the effective date (*e.g.,* update the PRS online forms to incorporate the new data elements, update the automated validation rules,

and revise the user guide and other documentation to reflect the requirements of the final rule). While the period of time between the effective date and compliance date remains as proposed, responsible parties can use the longer time between publication of the rule and the effective date to prepare for any submissions needed to comply with the final rule.

Commenters responded to the Agency's proposals on how clinical trial records at the time of the effective date of the rule would be handled. They disagreed with the approach to require results information for all outcome measures to comply with the rule in situations for which results information for primary outcome measures were submitted prior to the effective date, but results information for other measures are neither due nor submitted until on or after the effective date. Commenters suggested that the NPRM proposal, which would require updating the previously submitted information, might be burdensome, and researchers may not have designed or budgeted for such updates.

Others opposed the requirement to comply with the rule when a trial was completed before the effective date and, regardless of its due date, results information was not submitted prior to the effective date. They highlighted burden and additional workload as reasons for their opposition. One commenter opposed application of the rule to ongoing trials, suggesting that it disrupts the investment-backed expectations in place during early development of studied products.

Other commenters outlined alternatives to the proposal, including that new registration provisions only apply to trials registered after the effective date, and that new results provisions only apply to new results posted after the effective date, and to clinical trials with completion dates after the effective date. Another commenter suggested the burden caused by the proposal when the First Subject First Visit or Primary Completion Date is before the effective date—reporting on these studies would require reworking to accommodate the new criteria. This commenter noted a particular burden on small entities and suggested that the rule only apply to studies with First Subject First Visit or Primary Completion Dates after the effective date. As mentioned above, we have simplified the requirements for information submission during the transition, and this is discussed in more detail below.

One commenter suggested that applying regulations retroactively does not comport with typical legal standards of due process that favor prospective, as opposed to retroactive, application. Another commenter noted that if NIH does apply the rule retroactively to previously registered trials, responsible parties may need more time to address updates. We have considered the effects of the requirements in the final rule and do not believe that there are any impermissible retroactive effects that flow from the final rule. We believe that the revised approach being adopted alleviates the concerns expressed by commenters in this regard.

While we received no comments suggesting that the handling of clinical trial records on and immediately after the effective date be made explicit in the regulatory text, we did receive comments indicating that the rules are confusing. To resolve that general concern, we have restructured the requirements for which applicable clinical trials must be registered, whether results information submission is required for a particular applicable clinical trial, and whether the applicable registration and results information submission requirements are those specified in section 402(j) of the PHS Act or are those specified in these regulations. In making these changes, our aim is to be as clear as possible about the obligations of responsible parties.

Final Rule

The final rule differs from the proposal the NPRM in two important ways. First, we have extended the effective date from 45 calendar days to at least 120 calendar days after filing for public inspection of this rule by the Office of the Federal Register. However, the compliance date will remain the same, at 90 calendar days after the effective date. Second, the rule simplifies the process for determining which applicable clinical trials and information are subject to the rule's reporting requirements. Specifically, the registration requirements that apply to an applicable clinical trial are determined by the date on which the trial is initiated (*i.e.,* the actual study start date as defined in § 11.10(b)(16)), and the results information submission requirements that apply to an applicable clinical trial are determined by the date on which the trial reaches its actual primary completion date. We believe that this framework provides a logical approach to registering and submitting results information, in that it relies on what are, in the simplest terms, and for purposes of section 402(j) of the PHS Act and these regulations, the start date and the primary completion date of a trial.

Under this approach, the registration and results information submission requirements that apply to any given applicable clinical trial also depend on whether the trial is of an approved, licensed, or cleared product, or an unapproved, unlicensed, or uncleared product. We have reconsidered the approach described in the NPRM (79 FR 69593) with respect to determining whether an applicable trial involves an approved, licensed, or cleared product, or whether it involves an unapproved, unlicensed, or uncleared product. For purposes of this final rule, the marketing status of a product will be determined based on its marketing status on the primary completion date. Thus, if a drug product (including a biological product) or a device product is approved, licensed, or cleared for any use as of the primary completion date, we will consider that applicable clinical trial to be a trial of an approved, licensed, or cleared product. Similarly, if a drug product (including a biological product) or a device product is unapproved, unlicensed, or uncleared for any use as of the primary completion date, regardless of whether it is later approved, licensed, or cleared, we will consider that applicable clinical trial to be a trial of an unapproved, unlicensed, or uncleared product.

As a result of this interpretation, whether results information submission is required for an applicable clinical trial of an unapproved, unlicensed, or uncleared product depends on whether the primary completion date for that trial falls before or after the effective date of the regulations. If it falls before the effective date, then no results information is required to be submitted for that applicable clinical trial, regardless of whether the product studied in that clinical trial is later approved, licensed, or cleared. If the primary completion date is after the effective date of the final rule, then results information submission is required as specified in the final rule.

We recognize that there are responsible parties who submitted results information pursuant to the provisions in sections 402(j)(3)(C) and (E) for applicable clinical trials of products that were not approved, licensed, or cleared at the time the trial was ongoing, but which were approved after the primary completion date. Notwithstanding the fact that, under the interpretation in the final rule, results information for these trials was not required to be submitted, we do not consider the results information for these trials to have been submitted

pursuant to section 402(j)(4)(A). Although the previously submitted information will remain in the PRS system and will be publicly available, it is not subject to either the provisions of § 11.60 regarding voluntary submissions or the requirements in § 11.64 with respect to updates and corrections of information. The Agency does, however, encourage responsible parties to update such previously submitted results information and would not consider such updates to be subject to the voluntary submission requirements in § 11.60.

The applicable registration and results information submission requirements are summarized in the following table:

APPLICABILITY OF REQUIREMENTS IN 42 CFR PART 11

Initiation date	Primary completion date	Registration information submission required?		Results information submission required?	
		Approved, licensed, or cleared products	Unapproved, unlicensed, or uncleared products	Approved, licensed, or cleared products	Unapproved, unlicensed, or uncleared products
On or before September 27, 2007	After December 26, 2007 and before Effective Date of Final Rule.	Yes, as specified in section 402(j)(2)(A)(ii) of the PHS Act.	Yes, as specified in section 402(j)(2)(A)(ii) of the PHS Act.	Yes, as specified in section 402(j)(3)(C) and section 402(j)(3)(I) of the PHS Act.	No.
After September 27, 2007 and before the Effective Date of the Final Rule.	Before Effective Date of Final Rule.	Yes, as specified in section 402(j)(2)(A)(ii) of the PHS Act.	Yes, as specified in section 402(j)(2)(A)(ii) of the PHS Act.	Yes, as specified in section 402(j)(3)(C) and section 402(j)(3)(I) of the PHS Act.	No.
After September 27, 2007 and before Effective Date of Final Rule.	On or after Effective Date of Final Rule.	Yes, as specified in section 402(j)(2)(A)(ii) of the PHS Act.	Yes, as specified in section 402(j)(2)(A)(ii) of the PHS Act.	Yes, as specified in 42 CFR part 11.	Yes, as specified in 42 CFR part 11.
On or after Effective Date of Final Rule	On or after Effective Date of Final Rule.	Yes, as specified in 42 CFR part 11.	Yes, as specified in 42 CFR part 11.	Yes, as specified in 42 CFR part 11.	Yes, as specified in 42 CFR part 11.

The table above does not apply to voluntary submissions under § 402(j)(4)(A) of the PHS Act and § 11.60. The registration and results information submission requirements for the voluntary submission of clinical trial information are addressed in § 11.60.

We recognize that there will be some situations that arise in the months leading up to and following the effective date where a responsible party's obligations may shift depending on a variety of factors. For example, there may be a small number of applicable clinical trials for which the study start date (*i.e.,* the date of initiation) changes after the trial is registered and that that change may result in a shift in the registration and/or results information submission requirements for that applicable clinical trial. For example, if a responsible party initially registered an applicable clinical trial two months before the effective date of the final rule and entered an estimated study start date that fell one month before the effective date of the final rule, the responsible party's understanding at the time of registration would be that it would need to submit registration information as specified in section 402(j)(2)(A)(ii) of the PHS Act. However, if the trial is not initiated until after the effective date of the final rule, the responsible party will be required to comply with the registration provisions as specified in the final rule and to update the registration information for that applicable clinical trial. In a situation such as this, we would expect clinical trial registration information to be updated promptly, but in any case no later than as required under § 11.64(a) of the final rule. We note that in this scenario the responsible party will have been on notice since the publication date of the final rule both that the registration requirements will be changing as of the effective date and what those changes will be.

Similarly, if a responsible party initially registered an applicable clinical trial two months before the effective date of the final rule and entered an estimated study start date that fell one month after the effective date of the final rule, the responsible party's understanding at the time of registration would be that it would need to submit registration information as specified in the final rule (although we note that, because of the work needed to update the *ClinicalTrials.gov* data bank to accommodate the changes in the final rule, it may not be possible to enter information required as specified in the final rule prior to the effective date). However, if the applicable clinical trial actually was initiated one week before the effective date of the final rule, the trial would instead be subject to the registration requirements as specified in section 402(j)(2)(A)(ii) of the PHS Act and not the final rule.

Further, it is our understanding that, because of the complexities of how clinical research activities are managed at larger institutions, in some situations an applicable clinical trial might have been initiated but the individual who is responsible for submitting registration information regarding that trial might not have received notice of that initiation. If this scenario were to occur shortly after the effective date of the final rule, it is possible that the trial would be registered under the assumption that the requirements in the final rule apply and, therefore, more clinical trial information would be submitted than would be required. In this situation, the responsible party would not be required to update that additional registration information (although the information itself would remain available in the PRS system).

We also recognize that because a responsible party has 21 days after

initiation in which to register an applicable clinical trial, it is possible that a trial might be initiated before the effective date of the final rule but the responsible party might not submit registration information for it until after the effective date of the final rule. In this situation, notwithstanding the fact that the registration information for that applicable clinical trial was submitted after the effective date of the final rule, the Responsible Party would only be required to submit registration information as specified in section 402(j)(2)(A)(ii) of the PHS Act, not the final rule.

We appreciate that the possibility that situations such as these may arise will be of concern to affected responsible parties, and we are committed to assisting them in understanding their responsibilities and determining which requirements apply to particular applicable clinical trials. We would like to emphasize, however, that it has been clear since the proposed rule was issued in 2014 (and, in our view, since the enactment of FDAAA, with both its requirement that the rulemaking address the issue of results information submission and the provision that the Secretary may modify the registration requirements) that changes to the registration and results information submission requirements were both possible and highly probable.

While we believe that the NPRM provided a logical approach for handling records in transition, we understand that the approach might have been confusing to responsible parties. We believe that these changes will address the concerns of many commenters, such as those who did not believe primary outcome measures should have to be resubmitted when secondary outcome measures were due and submitted after the effective date. This change is simpler and clearer for those who were compliant under section 402(j) of the PHS Act. In addition, with the change to a later effective date, responsible parties who are subject to the registration and/or results information submission requirements in the final rule will have more time to plan accordingly.

V. Regulatory Impact Statement

The Agency has examined the impacts of this final rule under Executive Order 12866, Regulatory Planning and Review, Executive Order 13563, Improving Regulation and Regulatory Review, the Regulatory Flexibility Act (5 U.S.C. 601–612) (RFA), the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4), and Executive Order 13132, Federalism.

Executive Order 12866, as amended by Executive Order 13563, directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). A regulatory impact analysis must be prepared for major rules with economically significant effects ($100 million or more in any single year). The Agency estimates that the total cost of the requirements to regulated entities is approximately $59.6 million annually. We anticipate the potential for significant scientific and public health benefits, in the form of improvements in clinical trial designs, human subjects' protections, and improved evidence base to inform product development and clinical care. In addition, enhanced access to information about clinical trials may increase public trust in the research enterprise. We estimate that this rule is not an economically significant regulatory action as defined by Executive Order 12866. Because of the interest in this rule among regulated entities and others involved in conducting or using the results of clinical trials, we have, nevertheless, prepared an analysis that, to the best of our ability, estimates the costs and benefits of this rule. The RFA requires agencies to analyze regulatory options that would minimize any significant impact of a rule on a substantial number of small entities. The rule is estimated to impose costs of approximately $17,907 per applicable clinical trial (see Table 1 and Section V.G for additional information). Based on the RFA analysis (see Section V.G), we estimated that most small entities would be expected to be responsible for no more than one applicable clinical trial per year and that the per applicable trial cost to them would in general represent a small fraction of their revenues. This analysis forms the basis of the Agency's certification that the final rule will not have a significant economic impact on a substantial number of small entities.

Section 202 of the Unfunded Mandates Reform Act of 1995 requires, among other things, that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing ''any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year'' (2 U.S.C. 1352(a)). The current threshold, adjusted for inflation using the 2015 Implicit Price Deflator for the Gross Domestic Product, is $146 million. The Agency does not expect this rule to result in any 1-year expenditure that would meet or exceed this amount. As explained above, however, the Agency has conducted an analysis of the costs that could result from this rule.

Executive Order 13132 (Federalism) establishes certain requirements that an Agency must meet when it promulgates a proposed rule (and subsequent final rule) that imposes substantial direct requirement costs on State and local governments, preempts State law, or otherwise has Federalism implications.

A. Comments and Response

Commenters responded to the economic analysis in the NPRM of the estimates of the costs and benefits of the rule. While some commenters found the analysis appropriate overall and considered a 40 hour estimate for results information submission to be accurate, other commenters suggested that the time estimates used to calculate registration, results, and updates burden were lower than they should be. Some argued that the burden of entering information into the database is greater for smaller research institutions because, unlike larger research organizations, they are less likely to have dedicated and trained personnel to manage clinical trial information reporting. Others suggested the rule will be equally burdensome to small and large organizations. We recognize that some members of the regulated community may spend more hours than others to develop, process, and maintain clinical trial records. However, we believe our estimates of 8 hours for registration information, 40 hours for results information and 16 hours for updates of information are a reasonable representation of the overall average time required to complete all registration and results requirements by all respondents.

Commenters also suggested that *ClinicalTrials.gov* harmonize its clinical trial reporting requirements with existing international regulations in order to decrease the burden on institutions. It was suggested that reporting unique numbers of individuals with adverse events by organ system differs from the EU reporting standards and increases the burden of the rule. In consideration of the commenters' concerns, the final rule no longer requires the reporting of numbers of people with adverse events at the organ system level. We anticipate

that this change will decrease the burden of the rule.

One commenter suggested that the rule would also have an economic impact on biopharmaceutical development because of competitive harms associated with premature disclosure of confidential commercial information. As discussed in Section III.B of this preamble and § 11.44, this rule requires only summary level results information to be submitted, and it allows for delayed submission with certification in order to minimize any perceived competitive disadvantages for unapproved, unlicensed, or uncleared products (see § 11.44(b) and (c)) and delayed posting of registration information for unapproved or uncleared device products (see § 11.35(b)(2)(i)). Submission of clinical trial results information for applicable clinical trials of approved, licensed, or cleared products and applicable clinical trials of unapproved, unlicensed, or uncleared products, according to deadlines established by the final rule, ensures consistent and timely public access to comprehensive summary results for all applicable clinical trials. Furthermore, we are not persuaded that economic harms will result from the public posting of the required data elements.

Commenters also suggested that the cost estimates understated the burden associated with bringing previously submitted registration information into compliance with the final rule. One commenter suggested that the cost of compliance will not go down over time, while another suggested that in order to decrease this burden, the rule should only apply to those trials that had their First Subject First Visit or Primary Completion Date after the effective date of the rule. In consideration of commenters' concerns, the final rule eliminates virtually all additional burden associated with updating previously submitted trial information by requiring only registration as specified in the final rule for applicable clinical trials for which the date of initiation is after the effective date of the final rule and by only requiring results information submission as specified in the final rule for applicable clinical trials that reach their primary completion date after the effective date of the final rule. In light of these changes, which are discussed in more detail in Section IV.F of this preamble, there are very few applicable clinical trials registered or submitted partial results prior to the effective date of the final rule that will need to be updated as a consequence of the rule. As such, we expect the burden associated with such situations to be minimal because they will arise relatively infrequently. In addition, we anticipate that the occurrence of such situations will decrease over the next three years because, ultimately, there will be very few ongoing applicable clinical trials that were initially registered prior to the effective date of the final rule.

Another commenter suggested that the correction procedures proposed in § 11.66 could cause further economic burden because they thought that no clear distinction in the definitions of errors and falsifications was provided, which they said could lead to unnecessary and costly preemptive actions by the responsible party. The final rule no longer distinguishes between different types of errors (see § 11.64), and, thus, the potential economic burden of differentiating the type of error has been eliminated.

Commenters also suggested that the Agency should calculate actual burden and include other costs such as reprograming of institutional systems, increased medical review, and management oversight. They suggested that we had not sufficiently considered the costs associated with activities carried out by organizations that may invest substantial resources to avoid the negative consequences of violating the legal and regulatory requirements, *e.g.,* loss of federal grant support and/or monetary penalties. We agree that our cost estimate did not attempt to isolate the cost and burden that an institution as a whole might absorb in order to facilitate and monitor compliance among clinical investigators subject to the rule who are employed by the institution. Because overhead costs (*i.e.,* costs not related to direct labor or direct materials) varies among different industries and occupations, we attempted to approximate those overhead costs by doubling the average hourly wages in the personnel cost calculations. We took this approach in part because the cost of this rule is likely to vary significantly among institutions and organizations due to differences in institution's sizes, frequency of clinical trials performed per year and variation in the need to update or create information technology tools or application used to support clinical trial registration and results information submission and also because of the lack of data on the cost of institutional compliance. Nonetheless, in response to public comments, we have developed a separate estimate of the costs that institutions may assume in order to facilitate and monitor compliance among employees with responsibilities under the rule. The estimate is described in Section E below.

Commenters suggested that the Agency should allow financial burden of registration and results reporting to be covered as a direct cost in grants, whether incurred by the investigator or shared with a central administration unit. The Agency has previously clarified for NIH awardees that ''[g]iven the nature of registration and result information report requirement and that the project staff will generally be in the best position to submit and maintain these data, the costs of compliance with section 402(j) of the PHS Act will be generally allowable as direct charges to NIH grants. While it is expected that these costs will be covered by the funds provided with the grant, administrative supplements could also be considered'' [Ref. 112].

B. The Final Rule

The final rule codifies in federal regulation the provisions for the mandatory registration and submission of results information for applicable clinical trials to *ClinicalTrials.gov*, as required by section 402(j) of the PHS Act. This rule both clarifies the existing statutory requirements for submission of registration and results information, including adverse events information, and implements the expansion of the registry and results data bank by rulemaking as required by section 402(j)(3)(D) of the PHS Act.

C. Need for the Final Rule

The Agency is promulgating this rule to fulfill the requirements of section 402(j) of PHS Act in a manner that will provide broad public access to pertinent clinical trial registration and results information. Section 402(j)(2)(A)(i) of the PHS Act requires the Secretary to expand the clinical trials registry data bank with respect to clinical trial information to ''enhance patient enrollment and provide a mechanism to track subsequent progress'' of the clinical trials. Sections 402(j)(3)(B) and 402(j)(3)(C) of the PHS Act instruct the Secretary to expand the clinical registry data bank not later than 1 year after enactment of FDAAA to include the results information specified in section 402(j)(3)(C) for certain applicable clinical trials. Section 402(j) of the PHS Act also requires responsible parties to submit to the expanded data bank specified registration information (*i.e.,* descriptive information, recruitment information, location information, and administrative information) summarizing key aspects of applicable clinical trials that are subject to the law and specified results information

describing the outcomes of applicable clinical trials for which the drugs or devices under study have been approved, cleared, or licensed by FDA. Section 402(j) of the PHS Act further establishes deadlines by which such information must be submitted and establishes penalties for non-compliance. This final rule implements the statutory requirements and clarifies the Agency's interpretation of them. It explains the meaning of terms defined in the section 402(j) of the PHS Act (*e.g.,* responsible party and applicable clinical trial) and of several data elements that are required to be submitted to the data bank (*e.g.,* study design, eligibility criteria). It also exercises the authority given to the Secretary in section 402(j)(2)(iii) of the PHS Act to modify by regulation the requirements for clinical trial registration information. This final rule specifies several modifications to the clinical trial registration information that the Agency believes meet the statutory criteria of improving and not reducing the statutorily specified clinical trial registration information.

In addition, this rule is necessary to implement provisions of section 402(j) of the PHS Act that are specifically required to be addressed by regulation. Section 402(j)(3)(I) of the PHS Act, requires the Secretary to determine by regulation the ''best method'' for including in the registry and results data bank appropriate results information on serious adverse and other adverse events collected for certain applicable clinical trials. Section 402(j)(3)(D) of the PHS Act requires, among other things, the Secretary to further expand the registry and results data bank through rulemaking to ''provide more complete results information and to enhance patient access to and understanding of the results of clinical trials.'' Section 402(j)(3)(D) of the PHS Act specifies several topics that the rule is to address, including whether to require the submission of results information for applicable clinical trials of drugs and devices that have not been approved, licensed, or cleared by FDA; whether technical or lay summaries of a clinical trial can be included in the data bank without being misleading or promotional; and whether to require responsible parties to submit the protocol or ''such information on the protocol . . . as may be necessary to help evaluate the results of the trial.'' This rule addresses each of these topics and others specified in section 402(j) of the PHS Act.

D. Benefits of the Final Rule

As discussed in Section I of this preamble, the overarching aim of the final rule is to provide public access to a standardized set of information describing the conduct and results of certain clinical trials of FDA-regulated drugs (including biological products) and devices. Access to clinical trial information has significant scientific, and public health benefits, which we describe in Section I. These benefits accrue to potential and enrolled clinical trial participants, clinical researchers, systematic reviewers, disease and patient advocacy groups, regulators, drug and device manufacturers, healthcare providers, patients and their family members. Public access to clinical trial information can help patients find trials for which they might be eligible, enhance the design of clinical trials and prevent duplication of unsuccessful or unsafe trials, improve the evidence base that informs clinical care, increase the efficiency of drug and device development processes, improve clinical research practice, and build public trust in clinical research.

Access to clinical trial information assists individuals in finding trials in which they may be eligible to enroll. It can help people in making more informed decisions about participating in a clinical trial by providing them and their care providers with information about the results of a broader set of clinical trials of various interventions that have been studied for a disease or condition of interest. The highly structured data and search engine allows members of the public to search for trials for which they may be eligible [Ref. 19]. It also enables third parties to use the information describing the clinical trial to meet other specific needs [Ref. 35], such as reformatting the data for constituents of various patient advocacy groups (*e.g.,* patients with breast cancer) [Ref. 36], data mining for associations among interventions and diseases studied worldwide, and for use in semi-automated data collection for conducting critical appraisals and systematic reviews to support evidence-based medicine. For example, while *ClinicalTrials.gov* does not itself match potential participants with relevant trials, the rule ensures the timely posting of registration information about trials currently enrolling participants. This information is used by third parties to provide matching services that help patients find trials that might be appropriate for them.

Increased clinical trial transparency has the potential to drive scientific progress by informing future research, identifying knowledge gaps and opportunities, improving study designs, and preventing replication of unsuccessful trials and initiation of unsafe trials. Accessibility of clinical trial information may accelerate the drug discovery and development process by reducing redundancies and facilitating the identification and validation of new drug targets or surrogate endpoints, and it allows for improved understanding of the safety and efficacy of new therapies. The information provides a more robust evidence base for new research, which reduces systematic bias and leads to better science. Strengthening the evidence base also maximizes returns on the contributions of clinical trial participants as well as the time and financial investments of investigators, study funders, and sponsors.

Access to clinical trial information enables IRBs [Ref. 25], researchers, funding agencies, systematic reviewers [Ref. 26, 27], bioethicists [Ref. 28], science and public policy makers [Ref. 29], and others to see the landscape of trials on a given topic, by a particular funder, by geography [Ref. 30], by population [Ref. 9], or other relevant criteria. Providing these users with such a capability informs their judgments about the potential value of new trials. It also helps ensure that assessments of the risks and benefits of a potential intervention for a particular use reflect the totality of evidence from all prior trials. Such information also enhances scientific and financial accountability of sponsors. Landscape analyses such as these also provide feedback and insights for the clinical research community, by informing the design and analysis of future trials [Ref. 11, 31, 32].

Access to clinical trial results information helps fill substantial gaps in the database left by the non-publication (or very delayed publication) of a substantial portion of clinical trials in the medical literature [Ref. 42, 43]. Access to results from clinical trials of unapproved, uncleared, or unlicensed products is expected to alleviate the concerns regarding bias in the literature and selective publication. The complete set of results for all primary and secondary outcome measures supplements the more limited set of results data found in the published literature [Ref. 13, 37]. The availability of results information will help prevent the evidence base that is the foundation of systematic reviews and clinical practice guidelines from being skewed.

The availability of results information for trials of unapproved products may inform the assessment of risks and benefits that potential participants

might face in subsequent studies of those same or similar products; it may also contribute to the overall assessments that are made of similar marketed products [Ref. 46]. Trials of products that are unapproved, unlicensed, and uncleared are unlikely to be published if the results of these trials are insufficient to support applications for product approvals (*e.g.,* because the study resulted in negative findings or was inadequately designed or executed).

Clinical trials are expensive to initiate and carry out, and they are a significant national investment. Phase 2, 3, and 4 clinical trials cost on average, $13 million, $20 million, and $20 million respectively [Ref. 113], and it takes an average of $1.4 billion in clinical trial costs to develop 1 new compound [Ref. 114]. In FY 2016, NIH invested an estimated $3.3 billion in clinical trials and supportive activities [Ref. 115]. Access to more complete information about clinical trials helps conserve resources and, for federally funding trials, optimize the public investment in research. It helps avoid a suboptimal return on the financial resources invested by study funders and sponsors [Ref. 47] and can reduce costs by minimizing redundant trials.

Finally, another benefit of the rule is that it helps individual investigators, the clinical trial enterprise, and society as a whole fulfill an ethical obligation to trial participants. Individuals participate in clinical trials with the understanding that the research will contribute to the expansion of knowledge pertaining to human health. When trial information is withheld from public scrutiny and evaluation, the interpretation of the data and the public's trust in the research may be compromised. The rule helps to further the goal of ensuring that participation in research leads to accountability via the public reporting of information. The importance of trust in clinical research and public trust in the enterprise is promoted when we establish a public record of the trials in which people participate.

E. Costs Associated With the Final Rule

The costs associated with the final rule consist of the time and effort necessary for responsible parties to comply with the rule requirements to register applicable clinical trials; submit specified results information (including adverse event information); update and correct submitted registration and results information, as needed; submit certifications and/or extension requests to delay the deadline for submitting results information; submit information describing expanded access programs for drugs studied in an applicable clinical trial, and request waivers to any of the requirements for results information submission. We do not intend this rule to cause responsible parties to collect any information that was not already intended to be collected during the clinical trial, nor do we intend this rule to cause responsible parties to analyze such information in ways that were not intended under the protocol or the associated SAP. Rather, the rule specifies those elements of the collected results information that must be submitted to the data bank and the format in which that information must be submitted.

The calculations below present our estimates of the time and cost associated with meeting the information submission requirements of the final rule, including the burden associated with assembling the required information, formatting the information for submission, submitting it to the data bank, and correcting or updating it over time. The calculations break out the estimated annual costs associated with: (1) Registering a trial; (2) submitting results information; (3) submitting certifications, extension requests and appeals to delay the results information submission deadline; (4) submitting clinical trial information that is triggered by a voluntary submission; and, (5) creating expanded access records for drugs studied in an applicable clinical trial. The estimates include the costs associated with updating submitted information and with correcting errors detected by NIH. These are shown in the table below and, in the text below the table in Sections 1–5, we described these costs in more detail. We also estimate the costs of compliance to institutions that elect to devote resources to help investigators in their institutions who are subject to the rule to comply with its requirements. These additional resources mainly involve the hiring or reassignment of personnel to support the submission of registration and results information submission to *ClinicalTrials.gov*. The approach we took to estimate these costs is described below in Section 6. In the NPRM, we estimated cost of this final rule to be $32 million. Our higher estimate of $59.6 million is largely due to the more detailed consideration of costs that organizations may incur to ensure compliance on the part of responsible parties they employ.

1. Registration of Applicable Clinical Trials

To estimate the costs of trial registration, we first estimated the number of applicable clinical trials that would be initiated in a given year and be subject to the provisions of this final rule. Using the approach described below, we estimate that a total of 7,400 applicable clinical trials of drug products (including biological products) and device products per year would be subject to the registration requirement of this final rule. This estimate is based on information from FDA indicating that it receives approximately 5,150 clinical trial protocol submissions annually for applicable clinical trials (76 FR 256). This figure includes protocol submissions to CDER, CBER, and CDRH; it does not include clinical trials that were not conducted under an IND or IDE. To estimate the number of such clinical trials, we examined the number of clinical trials registered with *ClinicalTrials.gov* that appear to meet the criteria for an applicable clinical trial but do not appear to have been conducted under an IND or IDE, *e.g.,* because they are exempt from the requirement to submit an IND or IDE. We found approximately 1,700 and 2,000 such clinical trials in 2012 and 2013, respectively. We increased this figure to 2,250 to accommodate further growth in the number of such clinical trials that would be registered following publication of the final rule. The sum of these figures (*i.e.,* 5,150 plus 2,250 equals 7,400) provides an estimate of the number of applicable clinical trials that will be subject to the registration requirement of this final rule each year.

To calculate the burden associated with registering 7,400 clinical trials, we estimated the time required to submit complete clinical trial registration information for an applicable clinical trial. We estimate this time to be 8 hours, including time to extract information from the study protocol, reformat it, and submit it to *ClinicalTrials.gov*. This figure accounts for the estimated time needed to submit the 5 additional data elements that will be required by this final rule. Applying this time estimate to the estimated number of applicable clinical trials yields a burden of 59,200 hours per year for registering applicable clinical trials. Based on our previous experience, we estimate that each registration record will be updated an average of eight times during the course of the study (*e.g.,* to reflect changes in the conduct of the clinical trial, additions of investigational sites, recruitment status updates). Although clinical trials of long duration and with multiple sites will likely submit more updates during the course of the trial, we have found that many applicable clinical trials have a

relatively short duration and a limited number of study sites, which lowers the average per clinical trial. The time required for subsequent updates of clinical trial registration information is expected to be significantly less than for the original registration as less information must be provided) and is estimated to be 2 hours per update, resulting in a total of 16 hours of additional time attributed to updates per trial. Using these figures, we calculated the total annual hour burden for updates to clinical trial registration information for all applicable clinical trials to be 118,400 hours. Combining this figure with the estimated time for initial registrations (59,200 hours) yields an estimate of the total hour burden associated with the submission and updating of clinical trial registration information of 177,600 hours per year. These estimates include the time involved in addressing any issues identified during quality control review of submitted registration information.

To calculate the cost of registration, we examined May 2015 data from the U.S. Bureau of Labor Statistics on the average wages of life, physical, and social science workers in the pharmaceuticals and medicine manufacturing and medical scientists (except epidemiologists) also working in the pharmaceutical and medicine manufacturing industries. During the time we have operated *ClinicalTrials.gov,* we have found that this task is generally performed by junior-level researchers or administrative staff. For purposes of this estimate, we used an average hourly wage rate of $36.02, which is the average wage of life, physical, and social science workers in the pharmaceuticals and medicine manufacturing industries and is significantly higher than the median wage of other administrative staff in those sectors who are typically tasked with submitting registration information to *ClinicalTrials.gov*. Because overhead costs vary among different industries and organizations, we approximate overhead costs by doubling the average hourly wages (to $72.04 per hour). Using this adjusted wage figure, we calculated an estimated total annual cost of registration under the final rule, including updates over the course of a clinical trial, of $12,794,304 (Table 1). This figure represents an incremental increase of $533,096 per year above the estimated cost of registration prior to the rule.

2. Results Information Submission

To estimate the burden associated with submission of clinical trial results information, we started with the premise that every clinical trial required to register in a given year would be required subsequently to submit results information. The statute requires results information submission for all applicable clinical trials that study drugs (including biological products) or devices that are approved, cleared, or licensed by FDA. The rule requires, in addition, the submission of clinical results information for applicable clinical trials of drug products (including biological products) and device products that are not approved, cleared, or licensed by FDA. We, therefore, estimate the burden associated with results information submission for a total of 7,400 applicable clinical trials of drug products (including biological products) and device products per year, recognizing that in most cases, such clinical trial results information will not be submitted in the same year as the associated clinical trial registration information but in accordance with the deadlines specified in § 11.44. We expect, however, that on average the number of clinical trials for which clinical trial results information is submitted in any given year will approximate the number of new trials for which clinical trial registration information is submitted.

To estimate an average amount of time required to submit clinical trial results information, we reviewed a variety of data sources, including publicly available information from various organizations about results information submission times [Ref. 116], comments made at the April 2009 public meeting [Ref. 64], responses to the burden estimates included in the current and previous OMB clearance documents (77 FR 22579, Apr. 16, 2012; 73 FR 58972, Oct. 8, 2008), feedback from respondents who tested preliminary versions of the data entry system during the summer of 2008, and feedback from those submitting data to the existing *ClinicalTrials.gov* system. These sources contain a wide-range of estimates, from as little as 6 hours to as long as 60 hours. We believe the differences in these estimates reflect a number of factors, including the significant variation in the complexity of applicable clinical trials, in terms of the study design, number of outcome measures (primary and secondary), statistical analyses, and adverse event information. The estimates also reflect differences in the responsible party's familiarity with the clinical trial results information and the *ClinicalTrials.gov* submission process and the time they attribute to assembling the information for submission. Shorter estimates may be indicative of situations in which the responsible party already has assembled (and analyzed) the clinical trial results information for purposes of preparing a journal article or other summary report, while longer estimates may assume the clinical trial results information needs to be calculated and compiled. We expect that, in most situations, the responsible party would have ready access to the necessary information because it is information that the clinical trial is conducted to collect and analyze (*i.e.,* the information for submission would have been collected during the trial, as specified in the protocol). Nevertheless, for purposes of this analysis, we selected an average time of 40 hours for initial submission of clinical trial results information, which corresponds to the higher range of estimates contained in several industry surveys and in other comments the Agency received. This figure represents an increase of 15 hours over our 2015 estimate of 25 hours and reflects the additional information that is required to be submitted under this final rule. We expect the hour burden will decline as responsible parties become more familiar with *ClinicalTrials.gov* and implement procedures for streamlining data collection, analysis, and formatting.

This final rule requires submission of the full protocol and SAP (if a separate document) at the time results are submitted and allows redaction by the responsible party if confidential commercial information or personally identifiable information is included. Because protocol and SAP documents already exist, we do not expect that the requirement to upload them will impose a significant burden that is not already accounted for in the results submission burden. In addition, we anticipate that the need for redaction will be very rare, so those costs should also be minimal.

Prior to this final rule, we estimated that results information would be submitted for 3,700 applicable clinical trials per year, which is the estimated number of clinical trials that would have been included in marketing applications for drug products, biological products, and device products that were initially approved, licensed, or cleared by the FDA and subject to the basic results reporting provisions of section 402(j) of the PHS Act. Under the final rule, results information is required to be submitted as specified in the final rule for all applicable clinical trials that are subject to the registration requirement and that reach their completion date after the effective date of the final rule (*i.e.,* an

estimated 7,400 clinical trials per year). Applying the 40 hour figure to 7,400 applicable clinical trials per year produces a total estimated burden of 296,000 hours per year for submitting clinical trial results information. Our 2015 estimate was 92,500 hours.

We also estimated that, on average, each results record will be updated 2 times after the initial submission to reflect changes in data analysis or the submission of additional results from other pre-specified outcome measures (*e.g.,* submitting partial results). This estimate is based on user data collected to date, which indicates that each result record is updated, on average, 1.25 times after initial submission. We estimated that each such update will take 10 hours, on average. This figure is 2 hours over our 2015 estimate of 8 hours and reflects ongoing experience with data submission to *ClinicalTrials.gov.* Applying these estimates to 7,400 applicable clinical trials per year produces an estimate of 148,000 hours per year for updates to clinical trial results information (2 updates per trial), compared to 59,200 hours for the 3,700 applicable clinical trials estimated under the existing information collection. Combining the figure for updates with the estimate of the initial burden of submitting clinical trial results information, produces a total estimated annual hour burden for results information submission under the final rule of 444,000 hours, compared with 151,700 hours under the existing information collection. These estimates include the time involved in addressing any issues identified during quality control review of submitted results information.

To calculate the economic cost of clinical trial results information submission, we examined the average wages of workers in the pharmaceuticals and medical equipment industries who typically are involved in submitting clinical trial results information. Based on our experience in operating the results database and our consultations with data submitters, we believe that this task is performed generally by clinical researchers who are more experienced than those involved in registration. Based on May 2015 data from the U.S. Bureau of Labor Statistics, we identified the average hourly wage rate of $55.02, which corresponds to the mean hourly wage of a medical scientist (except epidemiologists) working in the pharmaceutical and medicine manufacturing industries. We doubled this wage rate (to $110.04) to account for benefits and overhead. Using this adjusted wage rate, we estimate a total annual cost of results information submission under this final rule, including updates, of $48,857,760 (Table 1). This represents an increase of $32,162,692 per year over our 2015 estimate of $16,693,068.

3. Delayed Submission of Results via Certification or an Extension Request

We also have estimated the average time and cost associated with the submission of certifications and extension requests to delay results information submission, consistent with § 11.44(b), (c) and (e). Responsible parties for applicable clinical trials may submit a certification to delay results information submission for an applicable clinical trial provided that initial approval, licensure, or clearance or approval, licensure, or clearance of a new use for the studied product is sought. We estimate that the number of clinical trials that will qualify for delayed submission of results in a given year will not exceed the estimated number of newly initiated applicable clinical trials per year that are conducted under an IND or IDE. Such clinical trials study drug products (including biological products) and device products that are unapproved, unlicensed, or uncleared or that are already approved, licensed, or cleared for one use but are seeking approval, licensure, or clearance of a new use. While some responsible parties might elect to submit clinical trial results information 1 year after the primary completion date instead of certifying for delayed submission, for purposes of this estimate, we assume that they all will elect to submit a certification to delay results information submission. (Note that the subsequent burden of submitting clinical trial results information is captured by the calculations in Section 2 above.) Using the same FDA data we used to estimate the number of applicable clinical trials subject to the registration requirements of this final rule, we estimate that certifications will be submitted for 5,150 trials per year. We estimate that it will take no more than 30 minutes for a responsible party to determine that an applicable clinical trial is eligible for a certification (and to verify the eligibility with a sponsor or manufacturer, if necessary) and to submit the necessary information to *ClinicalTrials.gov*. Using this figure produces an estimated annual hour burden of 2,575 hours for certifications. We estimate that the hourly wage of personnel who would submit the certification is the same as that for submitting clinical trial results information, or $55.02. Doubling this wage rate to account for benefits and overhead produces an annual estimated cost of $283,353 per year.

To estimate the number of good-cause extension requests, we considered several factors, including the rate of submission of requests between 2008 and 2015. A total of 192 requests were submitted during those 8 years (*i.e.,* 24 requests per year on average). Many of these requests were not needed in order to delay results information submission because the estimated primary completion date of the applicable clinical trial had changed. An extension request is not needed in such these situations because a responsible party need only update the estimated primary completion date to reflect changes in the progress of the trial. Other extension requests were submitted for clinical trials that were not applicable clinical trials subject to section 402(j) of the PHS Act. Under the rule, the approach outlined in § 11.22(b) and described in Section IV.B.2 of this preamble can be used to determine that the clinical trial is not an applicable clinical trial that is subject to this final rule. When these unnecessary requests are excluded, we received about 20 requests per year to delay results information submission for applicable clinical trials for which the actual primary completion date had passed. We have not attempted to estimate the number of responsible parties who may have thought they had a good cause for delaying submission but, rather than seeking the extension, chose instead to not submit results on time.

Under the final rule, we expect that the number of extension requests will increase as responsible parties gain more clarity about the deadlines for submitting clinical trial results information. We, thus, estimate that approximately 200 requests will be submitted per year, which represents a 10-fold increase over the annual rate of submissions to date. The estimated 200 requests is equivalent to 3 percent of all applicable clinical trials for which clinical trial results information is to be submitted in a given year (*i.e.,* 200 out of 7,400). It also represents about 10 percent of the applicable clinical trials that do not certify for delayed results information submission. We believe the 10-fold increase will also account for any responsible parties who will now seek an extension rather than simply not submitting results on time. While responsible parties may request an extension request even after they have filed a certification, we do not expect this to happen frequently. Moreover, as explained in Section IV.C.3 of this preamble, we expect that extensions will be granted in only a limited set of

circumstances where ''good cause'' has been demonstrated. In cases where an extension request is denied, the responsible party will have the opportunity to appeal the denial. If we estimate that 50 percent of extension requests are denied and that 50 percent of denials result in an appeal, we expect to receive 50 appeals per year.

We estimate that the time required for gathering the information for a good-cause extension request or appeal and submitting it to *ClinicalTrials.gov* will be no more than 2 hours. Using this figure, we estimate that the annualized hourly burden for extension requests and appeals will be 500 hours. We expect that requests will be submitted by individuals familiar with the results information submission requirements and, therefore, use an hourly wage of $55.02. Doubling this wage rate (to $110.04) to account for benefits and overhead brings the annualized cost of extension requests to $55,020. Combining the estimated costs for certification and extension requests produces a total cost of $338,373 per year (Table 1). Prior to the rule, we estimated that 3,700 certifications would be submitted by responsible parties seeking initial approval, licensure, or clearance or approval, licensure, or clearance of a new use of a drug product (including biological product) or device product studied in an applicable clinical trial and that 200 extension requests would be submitted per year. These figures yield an estimated annual cost of $245,114 meaning that the incremental cost attributable to this rule is $93,259 per year.

We note that under § 11.54, responsible parties may also seek a waiver from any applicable requirement of the rule. Such waivers are available only under extraordinary circumstances that must be consistent with the protection of the public health or in the interest of national security. We expect the need for such waivers to be exceedingly rare. As such, we are subsuming the costs of waiver requests in the extension request estimates.

4. Triggered Submission of Clinical Trial Information Following a Voluntary Submission

Section 11.60 of the final rule implements section 402(j)(4)(A) of the PHS Act and stipulates that if a responsible party voluntarily registers or submits results information for a clinical trial of an FDA-regulated drug product or device product that is not an applicable clinical trial subject to the mandatory clinical trial information submission requirements, that responsible party must, under specified circumstances, also submit information for other applicable clinical trials that are included in a marketing application or premarket notification that is submitted to FDA and for which clinical trial information has not already been submitted to *ClinicalTrials.gov*. The types of trials for which the voluntary submission of clinical trial information would invoke this requirement include, *e.g.,* phase 1 trials of drug products, small feasibility studies of device products (neither of which is considered to be applicable clinical trial) or applicable clinical trials that are not otherwise subject to section 402(j) of the PHS Act because they were initiated prior to the date of enactment of FDAAA and were no longer ongoing as of December 26, 2007. The voluntary submission of clinical trial information for such trials will trigger a requirement to submit clinical trial information for other applicable clinical trials that are included in the marketing application for a drug product or device product only if the entity submitting the marketing application or premarket notification is the same as the responsible party for those other trials and still has access to and control over the necessary data.

In practice, we expect that the requirement under section 402(j)(4)(A) of the PHS Act to submit clinical trial information for applicable clinical trials not otherwise registered in *ClinicalTrials.gov* will be triggered infrequently. In most cases, when clinical trial information is submitted voluntarily, we expect that the applicable clinical trials required to be submitted in a marketing application that includes the voluntarily-submitted clinical trial would be registered in *ClinicalTrials.gov* consistent with section 402(j)(2)(C) of the PHS Act and § 11.60. For example, the voluntary submission of information for a phase 1 trial of an unapproved drug product would trigger the submission of information for an applicable clinical trial that was not previously submitted only if the responsible party for the voluntarily-submitted trial is the same as the entity submitting the marketing application, the applicable clinical trial is required to be submitted in that marketing application, and the marketing application is for the same use studied in the voluntarily submitted trial. For purposes of this analysis, we estimate that 1 percent of the clinical trials registered voluntarily with *ClinicalTrials.gov* each year could trigger the submission of clinical trial information for an applicable clinical trial for which clinical trial information was not otherwise required to be submitted to *ClinicalTrials.gov.* Of the 19,170 clinical trials that are registered every year, on average, with *ClinicalTrials.gov,* we estimate that 11,770 are voluntary or do not fall under the rule (*i.e.* non-regulated) submissions (all but the 7,400 that are applicable clinical trials). Using 1 percent estimate and this figure, we calculate that voluntary registrations will trigger the required submission of clinical trials information for an estimated 118 clinical trials per year. Based on our experience to date with voluntary submissions, we expect that for at least three-quarters of those triggered trials (88 total) registration information only will need to be submitted; for the other quarter, results information will need to be submitted. For those clinical trials for which only registration information is required, we estimate that it will take a data submitter with an average hourly wage rate of $36.02 (consistent with the figures used for registration of applicable clinical trials) 8 hours to register the clinical trial. Doubling the wage rate to account for benefits and overhead produces an estimated cost of $50,716 per year. Submitted information will not generally need to be updated because the clinical trial will, in general, have reached its primary completion date by the time the requirement to submit clinical trial information is triggered. For the remaining quarter of the triggered clinical trials (30 total), we estimate that the hourly burden would equal the 40 hours estimated for results information submission for other applicable clinical trials plus 5 hours to account for the additional data elements that are specified in § 11.60(b)(2)(i)(B) and (c)(2)(i)(B). Using these figures and doubling the estimated average hourly rate of $55.02, we estimate the annual cost of submission as $148,554. Combining this figure with the $50,716 figure for triggered clinical trials that submit only registration information produces a total annual estimated cost of $199,270 for the submission of clinical trial information triggered by the voluntary submission of information under § 11.60 (Table 1). Because the submission of clinical trial information triggered by the voluntary submission of information was not required prior to the rule, the incremental cost attributable to this rule will be the full estimated cost of $199,270 per year. We note that each year a number of studies will likely be registered in *ClinicalTrials.gov* that are not subject to section 402(j) of the PHS Act.

Investigators may choose to register such studies in order to assist in the recruitment of subjects or to follow other policies, *e.g.,* scientific journal publication requirements, or for other reasons. Examples of such studies include studies of surgical or behavioral interventions. It is also possible that investigators may choose to register studies and report results information for clinical trials not subject to section 402(j) of the PHS Act because the final rule may bring about greater awareness of the registration or results information submission process.

Because we are not able to distinguish the portion of voluntary submissions of information to the database attributed to increased awareness of the final rule, the cost to entities that submit clinical trial information, but are not required to do so under section 402(j) of the PHS Act, as implemented by this final rule, are not included in this cost estimate. We do, however, account for them in the discussion of the PRA clearance of the requirements under this rule because we expect submissions to increase as a result of some combination of this rule and the contemporaneous NIH policy document, both of which are associated with the same OMB control number.

5. Expanded Access Records

As specified in § 11.28(a), if an expanded access record is available for an investigational drug product (including a biological product) that is studied in an applicable drug clinical trial, the responsible party for that applicable clinical trial must, if it is both the manufacturer of the investigational product and the sponsor of the applicable clinical trial, include the NCT number of the expanded access record with the clinical trial information submitted at the time of registration. If an expanded access record for the investigational drug product (including a biological product) being studied in the applicable clinical trial has not yet been submitted to *ClinicalTrials.gov*, and if the responsible party is both the manufacturer of the investigational product and the sponsor of the applicable clinical trial, the responsible party must create an expanded access record by submitting data elements in § 11.28(c). To determine the cost and burden associated with the creation of this record, we relied on information from FDA. Each year, an estimated 135 investigational drug products (including biological products) that were not previously available for expanded access use will be made available for individual patient expanded access (including emergency use) by responsible parties who are required to create an expanded access record. FDA estimates that 10 treatment INDs or treatment protocols are initiated annually and that expanded access use for intermediate size patient populations is initiated 68 times annually. These are the three types of expanded access for which information in § 11.28(c) must be submitted to *ClinicalTrials.gov* under this final rule for an expanded access record. We estimate the time required to submit the required information for an expanded access record to be 2 hours, which is one-quarter of the estimated time to register an applicable clinical trial. Compared to the number of data elements required under the rule for applicable clinical trials, only about half as many data elements are required for an expanded access record for expanded access use under treatment INDs, treatment protocols and for intermediate-size patient populations, and still fewer for expanded access records for individual patient expanded access use. The rule also does not require some of the more detailed data elements, such as Primary Outcome Measure, Secondary Outcome Measure, Individual Site Status, and Facility Location information. We also estimate an average of 2 updates per expanded access record per year, each taking which 15 minutes. We estimate the total hour burden associated with 213 expanded access records (*i.e.,* 135 investigational drug products available for single patient access, 68 for intermediate size patient populations and 10 treatment INDs or treatment protocols) to be 533 hours per year (426 hours for initial information submission plus 107 hours for information updates). We expect that expanded access records are submitted by staff with the same qualifications as those registering applicable clinical trials and, hence use an estimated hourly wage of $36.02. Doubling this wage rate to $72.04 to account for benefits and overhead results in a total estimated annual cost of $38,361 (Table 1). Because the submission of expanded access records was not included prior to rulemaking, the incremental cost attributable to this rule is the full estimated cost of $38,361 per year.

6. Institutional Compliance Costs

Organizations such as academic institutions may decide to devote more resources to ensure that applicable clinical trials being conducted in their organizations are compliant with the final rule. They may elect to do so in order to avoid the consequences of non-compliance, which, for an organization receiving federal funding for the clinical trial, could include suspension of grant funding were there to be a finding of non-compliance. These additional resources would primarily involve additional staff support to help facilitate and monitor compliance on the part of responsible parties within the organization.

Institutions of higher education that receive federal funding generally cover compliance activities under indirect costs rates that are negotiated for each institution. Although the final rule may cause an increase in compliance costs, the increase is anticipated to be incremental. Institutions can obtain up to 26 percent of their administrative costs to pay for administrative support.

To estimate the costs that institutions may bear because of the final rule, we estimated the current compliance costs (FDAAA pre-rule). We first identified the number of industry and non-industry sponsors of probable applicable clinical trials (pACTs) who submitted results to *ClinicalTrials.gov* in 2015 and separated them into three categories based on volume of pACTs submitted per year. The categories were low volume, defined as 1 to 5 pACTs per year; medium volume, defined as 6 to 10 pACTs per year; and high volume, defined as 11 or more pACTs per year. We identified 363 non-industry sponsors (312 low volume, 29 medium volume, 22 high volume) and 277 industry sponsors (238 low volume, 17 medium volume, 22 high volume) who submitted pACT results information in 2015. We then multiplied the current number of full time employees (FTEs) per organization, a figure estimated to be 0.5 FTEs [Ref. 117], by the total number of industry and non-industry sponsors who submitted pACT results information in 2015. We then multiplied the estimated total FTEs by the estimated annual salary costs, using U.S. Bureau of Labor Statistics data on average wages from May 2015 of medical scientists (except epidemiologists) in the pharmaceuticals and medicine manufacturing ($36.02 per hour) and medical scientists (except epidemiologist) in a college, university or professional school ($32.17 per hour). We doubled these wage figures (to $72.04 and $64.34) to account for benefits and overhead. The final total product of the FDAAA pre-rule institutional yearly cost of compliance for all sponsors was estimated to be $45 million (Table 1).

We next estimated the cost of the final rule and used reported number of compliance staff from a high volume sponsor [Ref. 118]. We assumed that the required number of FTEs will depend

on the number of trials to be overseen and thus estimated that low volume sponsors will need 0.5 FTEs. We assumed that, in most cases, low volume sponsors will not need to hire additional FTEs because reporting responsibilities will be fulfilled by the responsible parties themselves (as detailed and calculated in Sections 1–3 above). We also estimated that medium volume sponsors will need 2 FTEs and high volume sponsors will require an estimated 3 FTEs. We calculated the product of the total institutional cost with the adjusted increase in compliance staff is estimated to be $70.3 million (Table 1). The difference between the cost estimate of the final rule and the estimate of the amount spent currently on compliance (FDAAA pre-rule) is $25.2 million. We believe these estimates are likely to be overestimates because FTEs involved in FDAAA final rule compliance activities at many institutions will be engaged in other compliance activities that relate to other federal and state laws and regulations governing clinical research (*e.g.,* FDA IND/IDE and IRB regulations, Common Rule) as well as compliance activities due to non-governmental clinical trial-related policies (*e.g.,* journal editors require trial registration before the first participant is enrolled as a condition for the publication results after study completion) [Ref. 98]. We also assumed that the FTEs will spend some time up front engaged in developing programs or systems to facilitate institutional compliance efforts, and that they will later shift their focus to compliance monitoring activities. Therefore, the number of attributable FTEs is constant over time and the cost of updating existing IT programs/systems is already included. We also did not differentiate between industry and non-industry organizations to reflect the fact that industry organizations have well-established regulatory affairs operations, the functions of which include compliance monitoring and oversight. We believe that many of these operations are already engaged in oversight activities to support compliance with the statutory requirements. Thus, the costs for industry organizations are likely an overestimate.

We estimate the annualized cost to the Federal Government due to the final rule data collection requirements is approximately $1.4 million for *ClinicalTrials.gov* activities. This figure includes the increased cost associated with contractors required to develop software and operate the database and senior scientists, analysts, and other staff needed to carry out and oversee *ClinicalTrials.gov* operations as well as other costs including database equipment and maintenance.

We estimate the total annual cost of the final rule to be $59.6 million. We expect that over time the cost of complying with the final rule will decline notably as responsible parties become more familiar with the registration and results information submission requirements as well as the data submission and review processes. Many institutions may have already developed systems and procedures to support investigators in fulfilling their reporting responsibilities under the statute. Also, a number of clinical trial data management software tools currently allow users to output registration information for automatic uploading of files in bulk to *ClinicalTrials.gov.* We expect that by clarifying the requirements for submission of clinical trial in this final rule, responsible parties will automate portions of the data extraction and formatting processes for required results information, significantly reducing the burden and associated cost of compliance with this final rule.

TABLE 1—ESTIMATED ANNUAL COST OF FINAL RULE

Provision	Final rule section(s)	Estimated annual cost prior to rulemaking	Estimated annual cost under the final rule	Incremental cost above pre-rule data collection
Registration of applicable clinical trials, including updates	11.28(a),(b), 11.64(a).	$12,261,208	$12,794,304	$533,096
Results information submission for applicable clinical trials, including updates.	11.48, 11.64(a).	16,693,068	48,857,760	32,162,692
Submission of certifications, extension requests, and appeals to delay results information submission.	11.44(b), (c), (e).	245,114	338,373	93,259
Triggered registration and results information submission following voluntary submissions.	11.60	0	199,270	199,270
Submission of expanded access records	11.28(c)	0	38,361	38,361
Institutional compliance costs		45,042,920	70,287,277	25,244,357
Cost to the Federal Government		4,826,307	6,190,784	1,364,477
Total	N/A	79,068,617	138,706,129	59,635,512

F. Alternatives to the Final Rule

Section 402(j)(3)(D)(v)(VI) of the PHS Act requires the Secretary to promulgate regulations to expand the registry and results data bank and to address specific issues that are enumerated in the statute. Section 402(j)(2)(A)(iii) of the PHS Act also authorizes the Secretary to make additions or modifications to the statutorily enumerated requirements for registration of applicable clinical trials. This final rule implements and expands the basic provisions mandated by section 402(j) of the PHS Act that became effective prior to rulemaking on the schedule established by the statute. In the NPRM, we described various alternatives that we considered in exercising authority to add or modify the statutory provisions and in addressing the topics that were required to be addressed through rulemaking. In developing the final rule, and informed by public comments, we considered alternatives approaches that could be taken in the final rule. We discuss two here.

One important provision of the final rule requires results information from applicable clinical trials of unapproved, unlicensed, or uncleared products to be submitted. The Agency has concluded that the public health benefits of this approach, as discussed in above in Section D, justify the costs. In particular, trials of products that are unapproved, unlicensed, or uncleared are unlikely to be published if the

results of these trials would not help support applications for product approval, licensure, or clearance. This rule's requirements that responsible parties submit results information from applicable clinical trials of unapproved, unlicensed, or uncleared products regardless of whether approval, licensure, or clearance is sought, as well as the public posting of this information, are expected to help address bias in the literature and selective publication of results. The requirement for results information submission will make information public that otherwise likely would not have reached the public domain. The availability of results information from such applicable clinical trials will help to prevent the evidence base, which serves as a foundation for future research, systematic reviews, and clinical practice guidelines, from being skewed. The alternative position—not requiring results information submission for applicable clinical trials of unapproved, unlicensed, or uncleared products—would decrease the costs of the rule as estimated in Section V.E.2, but it would likely be costly to public health because of the absence of the benefits described in Section V.D. Therefore, the Agency believes that the benefits to public health justify the cost of compliance.

The final rule also requires submission of the final research protocol and SAP as part of the results information (discussed in Section III.D of the preamble). We expect the protocol to provide users of *ClinicalTrials.gov* with more complete information about the trial. One of the aims of section 402(j) of the PHS Act and of the rule is to ''provide more complete results information.'' We believe this goal complements the goals of increased transparency and accountability. As such, the submission of the protocol and SAP will provide more complete results information and significantly enhance the understanding of the trial and the context of the data fields provided. Because protocol and SAP documents already exist, we do not expect that the requirement to upload them will impose a significant burden that is not already accounted for in the results submission burden. The alternative—not requiring the submission of protocol—would have little to no effect in reducing the burden of the rule, but it would decrease public health benefits by decreasing the transparency of clinical trial results information.

G. Regulatory Flexibility Act

The RFA (5 U.S.C. 601–612) requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. This final rule will affect a number of small entities that conduct clinical trials of drug products and device products, but the Agency estimates that the costs incurred by small entities would be limited, especially in relation to the other costs associated with conducting a clinical trial. As explained below, the Agency believes that the final rule is not likely to have a significant economic impact on a substantial number of small entities.

The companies that would be affected by this final rule are classified in seven separate 2012 North American Industrial Classification System (NAICS) categories by the Census Bureau. The affected industries are NAICS 325412—Pharmaceutical Preparation; NAICS 325414—Biological Products (except diagnostic); NAICS 334510—Electromedical and Electrotherapeutic Apparatus; NAICS 339112—Surgical and Medical Instrument; NAICS 339113—Surgical Appliance and Supplies; NAICS 339114—Dental Equipment and Supplies; NAICS 339115—Ophthalmic Goods [Ref. 119]. The Small Business Administration (SBA) size standards define small entities as those companies with a maximum number of employees. The 2016 size standards for all these industries are shown in the table below [Ref. 120]. The most recent data from the U.S. Census of Manufacturers that offers the level of detail for establishments at or near the employee size limits as defined by SBA is from 2012 [Ref. 121]. In each of these establishment size categories, large majorities (*i.e.,* 90 percent or more) of the establishments meet the criteria as small entities [Ref. 122]. Even taking into account that many of these establishments are parts of multi-establishment corporations, significant numbers of companies would still qualify as small entities and have fewer than 100 employees across all of these categories (*i.e.,* ranging from 79 percent to 96 percent of all establishments within a category). Although the Agency expects that most companies sponsoring applicable clinical trials would be larger than the average-sized company in their industry, the Agency concludes that a substantial number of companies would still qualify as small entities.

TABLE 2—SIZE STANDARDS FOR AFFECTED COMPANIES

NAICS code and industry description	Size standards in number of employees
NAICS 339113—Surgical Appliance and Supplies	750
NAICS 339114—Dental Equipment and Supplies	750
NAICS 339112—Surgical and Medical Instrument	1,000
NAICS 339115—Ophthalmic Goods	1,000
NAICS 325412—Pharmaceutical Preparation	1,250
NAICS 325414—Biological Products (except diagnostic)	1,250
NAICS 334510—Electromedical and Electrotherapeutic Apparatus	1,250

The cost analysis presented above indicates an estimated cost of compliance with this final rule of $17,907 per applicable clinical trial ($132,515,345 for 7,400 clinical trials per year). While some larger firms could be the responsible party for multiple applicable clinical trials in the same year, we expect most small firms would be responsible for no more than one applicable clinical trial per year. Using data from the 2012 Census of Manufacturers, we used the average value of shipments for establishments in these industries to calculate the cost percentage of the rule on small entities. Assuming that small operations with one to four employees had one applicable clinical trial that was required to submit registration or results information each year, the costs of this final rule would representan estimated 3.4 percent of the annual value of shipments. For establishments with 50 to 99 employees, the costs of this final rule would represent an estimated 0.9 percent of the value of shipments, even

if they were responsible for 10 applicable clinical trials administered annually. For establishments with 100 or more employees, the costs of this final rule would represent an estimated 0.1 percent of the value of shipments even with 10 applicable clinical trials administered annually. Although the figure for establishments with one to four employees in one industry was estimated to be 3.4 percent at most, the remaining figures are well below the threshold of 3 to 5 percent of the total revenue for small entities needed to consider that this final rule would have a significant economic impact on a substantial number of small entities. The Agency concludes and certifies that this final rule would not have a significant economic impact on a substantial number of small entities.

In practice, we expect the burden on small firms will be significantly lower than this estimate. In general, the applicable clinical trials initiated by small firms will be less complex than the applicable clinical trials initiated by large firms, including, for example, fewer trial locations (sites), shorter duration, and fewer outcome measures. As a result, the amount of results information to be submitted—and the time and cost associated with such submissions—will be less than for larger entities and represent a smaller share of shipments. In addition, these costs would affect only a fraction of small firms in any given year. For example, by our estimates, registration information would be required to be submitted (and results information subsequently submitted) for approximately 500 applicable device clinical trials in any given year. Information from the 2012 Economic Census of the United States indicates that there are approximately 11,500 companies in the U.S. that are involved in the manufacture of medical devices and that almost 11,000 of them have fewer than 100 employees. Even if no company engaged in more than one applicable clinical trial at the same time, then on average, less than 10 percent of all device manufacturers would initiate a trial subject to the registration and results information submission requirements of this final rule in any given year (700 applicable device clinical trials per year divided by 11,500 firms equals 0.061 or 6.1 percent).

H. Unfunded Mandates Reform Act of 1995

Section 1352(a) of the Unfunded Mandates Reform Act of 1995 requires that the Agency prepare, among other things, a written statement that includes an assessment of anticipated costs and benefits before proposing ''any rule that includes any Federal mandate that may result in the expenditure by State, local, and Tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any 1 year'' (2 U.S.C. 1532(a)). The current threshold, adjusted for inflation using the 2015 Implicit Price Deflator for the Gross Domestic Product, is $146 million. We do not expect the direct burden of this final rule, including the cost of compiling, submitting, and updating clinical trial registration and results information for applicable clinical trials, to result in any 1 year expenditure that would meet or exceed this amount. Nor do we expect that State or local governments would bear a significant fraction of this cost, as most of the entities affected by the final regulation would be private entities. As a result, we conclude that this rule has no consequential effect on State, local, or tribal governments or on the private sector. We have determined that this final rule would not constitute a significant rule under the Unfunded Mandates Reform Act of 1995 because it would impose no mandates with costs exceeding the current threshold.

I. Federalism

Executive Order 13132, Federalism, establishes certain requirements that an Agency must meet when it promulgates a proposed rule (and subsequent final rule) ''that imposes substantial direct compliance costs on State and local governments,'' preempts State law, or otherwise has federalism implications. The Agency has analyzed this final rule in accordance with the principles set forth in Executive Order 13132 and has determined that this final rule does not contain policies that would impose any ''substantial direct compliance costs on State or local governments[.]'' This final rule, does, however, have federalism implications.

Section 801(d)(1) of FDAAA expressly provides a preemption provision as follows: ''Upon the expansion of the registry and results data bank under section 402(j)(3)(D) of the Public Health Service Act . . . no State or political subdivision of a State may establish or continue in effect any requirement for the registration of clinical trials or for the inclusion of information relating to the results of clinical trials in a database.'' We interpret this language to prohibit a State or political subdivision of a State from establishing any requirement for the inclusion of information in a database that is (1) clinical trial registration information, as that term is defined in § 11.10, *i.e.,* the actual registration data elements; (2) clinical trial results information required to be submitted under section 402(j)(3) of the PHS Act and this part; or, (3) information that is otherwise collected through any data element in ClinicalTrials.gov, such as information relating to voluntary submissions and other information whether or not required to be submitted under section 402(j) of the PHS Act and this part. We do not interpret section 801(d)(1) of FDAAA to preempt other types of reporting and/or data collection that States may require related to public health, disease surveillance, clinical care, or the practice of medicine such as patient and disease registries or public health surveillance registries.

VI. Paperwork Reduction Act of 1995

This final rule contains requirements that are subject to review by OMB under the PRA (44 U.S.C. 3501–3520). Sections 11.28, 11.48, 11.60, 11.62, and 11.64 of this rule contain information collection requirements that are subject to OMB approval. A revision of the 2015 PRA clearance for clinical trial registration and results information submission (OMB 0925–0586) to meet the requirements of this final rule will be submitted to OMB for review. It will also be updated to request approval to collect clinical trial registration and results information under a final policy that NIH is issuing in tandem with the final rule that will apply to all NIH-funded clinical trials, including those not subject to the rule [Ref. 65].

Section VII of the NPRM, the Agency provided an estimate of the annualized burden hours associated with the information collection requirements included in the proposed rule, and we invited comments on: (1) Whether the proposed collection of information is necessary for the proper performance of the functions of NIH, including whether the information will have practical utility; (2) the accuracy of the estimate of the burden of the proposed collection of information by NIH, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology (79 FR 69663). The comments we received are discussed in Section V.A of the final rule.

A description of the information collection requirements included in this rule is provided in the Regulatory

Impact Statement (Section V of this preamble) and is summarized in this section of the preamble with an estimate of the annualized burden hours. Included in this estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing, reviewing, updating, and correcting each collection of information.

Organizations and individuals desiring to submit comments on the information collection and submission requirements should send their comments by October 21, 2016 to (1) Ms. Mikia Currie, Project Clearance Officer, National Institutes of Health, Rockledge Centre 1, 6705 Rockledge Drive, Room 3509, Bethesda, Maryland 20817, telephone 301–594–7949 (not a toll-free number); and (2) the Office of Information and Regulatory Affairs, OMB, *OIRA_submission@omb.eop.gov,* or by fax to 202–395–6974, and mark ''Attention: Desk Officer for the National Institutes of Health, Department of Health and Human Services.'' After we obtain OMB approval, we will publish the OMB control number in the FR.

The estimate includes the annual hourly burden for submission, updating, and correction of information both for applicable clinical trials that are subject to this rule and for the larger number of clinical trials for which information is submitted to *ClinicalTrials.gov* on a voluntary basis in order to recruit subjects, remain eligible to publish summary articles in scientific journals that follow the guidelines of the ICMJE, to comply with NIH or other public, company, or other organizational policies regarding public disclosure of clinical trial information, or for other purposes.

The burden for trials that are subject to this rule follows the estimates presented in Section V of this preamble. For registration, we estimated 7,400 applicable clinical trials which included the number of clinical trials that would be subject to mandatory registration under the rule. This estimate reflects the number of protocols for applicable clinical trials that are submitted to FDA under an IND or IDE (*i.e.,* 5,150), as well as applicable clinical trials that are not conducted under an IND or IDE (*i.e.,* 2,250). We also increased the estimated hour burden of registration from 7 hours in the 2015 information collection, to 8 hours to reflect the additional data elements that would be required under this rule. For results information submission, we have increased from 3,700 to 7,400 our estimate of the number of applicable clinical trials that would be subject to mandatory results information submission under this rule. The final rule requires the submission of results information for all registered applicable clinical trials, regardless of whether or not the drug product (including biological product) or device product under study in the trial is approved, licensed, or cleared. We have made corresponding increases in the estimated number of applicable clinical trials for which a certification to delay results information submission would be submitted. We have also increased the estimated hour burden for submitting results information from 25 hours to 40 hours to account for the additional results information that would be required to be submitted under this rule. In addition, we have added estimates of the burden associated with the submission of registration and results information that could be triggered by some voluntary submissions of clinical trial information under § 11.60. Finally, we have included a separate estimate of the burden associated with the creation of an expanded access record if an investigational drug product (including a biological product) that is studied in an applicable clinical trial is available under expanded access. See figures in Table 3.

As we noted in Section V, a number of trials studies will likely be registered in *ClinicalTrials.gov* that are not subject to section 402(j) of the PHS Act. Investigators may choose to register such studies in order to assist in the recruitment of subjects or to comply with medical journal policies that make registration in a publicly accessible repository a condition of publication. In addition, starting in 2017, clinical trial registration and results information will also be collected from NIH-funded investigators whether or not they are subject to the final rule, which will lead to an increase in the number of non-regulated submissions.

In order to estimate the impact of the NIH policy, over and above the impact of the rule, we began by determining that 526 NIH funded trials that are likely not applicable clinical trials were first registered in 2015. These represent the likely number of trials that will have the additional burden of submitting results per year under the NIH policy. In addition, we estimated that approximately 25 percent of NIH-funded trials that are not applicable clinical trials have not been registered in the past (despite encouragement from NIH and the journal editors' policy). This leads to an estimate of an additional 131 trials registered and reporting results per year. The total number of non-applicable clinical trials that will register and submit results due to the NIH policy is estimated to be 657 per year. Investigators subject to the NIH policy will be expected to submit the same information within the same timeframes as parties subject to 402(j)(2)(C) of the PHS Act. We, thus, use the assumptions here that we used to estimate the burden for applicable clinical trials, *i.e.,* initial submission of registration information will take an average of 8 hours, updates of 2 hours apiece will take place 8 times during the course of the study and, initial results submission will take on average 40 hours with 2 expected updates requiring an average of 10 hours total. Adding the registration burden to the results information burden yields an estimated total annual hour burden of 55,188 (Table 3).

In order to estimate the burden for clinical trials that are not subject to section 402(j) of the PHS Act, including the requirements in this final rule, and will not be subject to the NIH policy, we examined registrations to *ClinicalTrials.gov* in calendar year 2015 and found that a total of 19,170 clinical trials were registered that year. Since we estimate that 7,400 of these are applicable clinical trials, the remainder 11,770 trials, can be considered voluntary or to not fall under the rule. Of these, 526 were NIH funded. This leaves an estimated 11,244 trials registered per year that do not fall under either the rule or the NIH policy.

We expect that these clinical trials will submit the same clinical trial registration information as is submitted for applicable clinical trials that are subject to the rule. We expect that information submitted for such clinical trials will be updated as frequently as information for applicable clinical trials that are subject to the rule. Therefore, for calculating the registration burden associated with these clinical trials, we use the same assumptions as for applicable clinical trials required to register under section 402(j)(2)(C) of the PHS Act, *i.e.,* initial submission of registration information will take an average of 8 hours, updates of 2 hours apiece will take place 8 times during the course of the study. Applying these figures yields an estimated annual burden of 269,856 hours, of which 89,952 derives from the initial registration and 179,904 derives from updates (Table 3).

For clinical trials that are not subject to section 402(j) of the PHS Act, including the requirements in this final rule, or the NIH policy, we expect that often only clinical trial registration information, and not both registration and results information, will be

submitted. To estimate the number results submissions will be submitted, we looked at results submissions in 2015 and found that 1,580 were for clinical trials that were neither applicable clinical trials nor funded by NIH. We estimate that this number will grow slightly, secondary to various other funder policies (*e.g.,* PCORI). We, therefore, estimate that we will receive approximately 2,000 results per year that are not due to either the rule or the NIH policy. We estimate that the time required to submit clinical trial results information for such clinical trials would be equivalent to that for applicable clinical trials required to register under section 402(j)(2)(C) of the PHS Act. Using those figures, we estimate that the total annual hour burden for submitting clinical trial results information for clinical trials that are not otherwise required to submit results information would be 80,000 hours, plus 40,000 hours for updates (Table 3).

TABLE 3—ESTIMATED BURDEN FOR REGISTRATION AND RESULTS INFORMATION SUBMISSION AT CLINICALTRIALS.GOV

Type of respondents	Number of respondents	Frequency of response	Average time per response (hours)	Annual hour burden
Regulated Submissions (Subject to this Rule)				
Registration	7,400	1 Initial	8	59,200
		8 Subsequent Updates	2	118,400
Results Information	7,400	1 Initial	40	296,000
		2 Subsequent Updates	10	148,000
Certifications to delay results submission	5,150	1	0.5	2,575
Extension requests and appeals	250	1	2	500
Registration triggered by voluntary submission.	88	1	8	704
Results triggered by voluntary submission	30	1	45	1,350
Expanded access records	213	1 initial	2	426
		2 Subsequent Updates	0.25	107
Subtotal for Regulated Submissions	627,262			
Non-regulated Submissions Related to the NIH Policy				
Registration	657	1 Initial	8	5,256
		8 Subsequent Updates	2	10,512
Results information	657	1 Initial	40	26,280
		2 Subsequent Updates	10	13,140
Subtotal for Non-regulated Submissions Related to the NIH Policy.	55,188			
Non-regulated Submissions				
Registration	11,244	1 Initial	8	89,952
		8 Subsequent Updates	2	179,904
Results information	2,000	1 Initial	40	80,000
		2 Subsequent Updates	10	40,000
Subtotal for Non-regulated Submissions	389,856			
Subtotal for Non-regulated Submissions and Submissions Related to the NIH Policy.	445,044			
Total	1,072,306			

VII. Legal Authority

These regulations are issued under the authorities contained in 42 U.S.C. 282(i); 42 U.S.C. 282(j); 5 U.S.C. 301; 42 U.S.C. 286(a); 42 U.S.C. 241(a); 42 U.S.C. 216(b); and sections 801(c)–(d), Public Law 110–85, 121 Stat. 921–922 (42 U.S.C. 282 (note)).

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List of Subjects in 42 CFR Part 11

Biologics, Clinical trial, Data bank, Drugs, Human subjects research, Medical devices, Medical research, Registry, Reporting and recordkeeping requirements, Results information.

Regulatory Text

For the reasons stated in this preamble, the U.S. Department of Health and Human Services amends Title 42, Chapter I of the Code of Federal Regulations by adding Part 11 to subchapter A to read as follows:

PART 11—CLINICAL TRIALS REGISTRATION AND RESULTS INFORMATION SUBMISSION

Subpart A—General Provisions

Sec.

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Authority: 42 U.S.C. 282(i); 42 U.S.C. 282(j); 5 U.S.C. 301; 42 U.S.C. 286(a); 42 U.S.C. 241(a); 42 U.S.C. 216(b).

Subpart A—General Provisions

§ 11.2 What is the purpose of this part?

This part implements section 402(j) of the Public Health Service Act (42 U.S.C. 282(j)) by providing requirements and procedures for the submission of clinical trial information for certain applicable clinical trials and other clinical trials to the Director of the National Institutes of Health (NIH) to be made publicly available via ClinicalTrials.gov, the Internet-accessible clinical trial registry and results data bank established by the National Library of Medicine (NLM) at *https://clinicaltrials.gov.*

§ 11.4 To whom does this part apply?

(a) This part applies to the responsible party for an applicable clinical trial that is required to be registered under § 11.22, a clinical trial for which clinical trial registration information or clinical trial results information is submitted voluntarily in accordance with § 11.60, or an applicable clinical trial that is required by the Director to have clinical trial information submitted to protect the public health under § 11.62.

(b) The responsible party must communicate the identity and contact information of the responsible party to the Director by submitting the Responsible Party, by Official Title and Responsible Party Contact Information data elements under § 11.28(a)(2)(iii)(B) and (a)(2)(iv)(F) as part of the clinical trial information submitted at the time of registration. Changes must be communicated to the Director by updating information in accordance with § 11.64(a).

(c) *Determination of responsible party.* For purposes of this part, each applicable clinical trial or other clinical trial must have one responsible party. With respect to a clinical trial, the sponsor of the clinical trial will be considered the responsible party unless and until a principal investigator has been designated the responsible party, in accordance with paragraph (c)(2) of this section. With respect to a pediatric postmarket surveillance of a device product that is not a clinical trial, the responsible party is the entity that the U.S. Food and Drug Adminstration (FDA), under section 522 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 3601), orders to conduct the pediatric postmarket surveillance of a device product.

(1) *Determination of sponsor.* For purposes of this part, each applicable clinical trial or other clinical trial must have one sponsor.

(i) When an applicable clinical trial or other clinical trial is conducted under an investigational new drug application (IND) or investigational device exemption (IDE), the IND or IDE holder will be considered the sponsor.

(ii) When an applicable clinical trial or other clinical trial is not conducted under an IND or IDE, the single person or entity who initiates the trial, by preparing and/or planning the trial, and who has authority and control over the trial, will be considered the sponsor.

(2) *Designation of a principal investigator as the responsible party.*

(i) The sponsor may designate a principal investigator as the responsible party if such principal investigator meets all of the following requirements:

(A) Is responsible for conducting the trial;

(B) Has access to and control over the data from the trial;

(C) Has the right to publish the results of the trial; and

(D) Has the ability to meet all of the requirements for submitting and updating clinical trial information as specified in this part.

(ii) With regard to an applicable clinical trial or other clinical trial, a designation by the sponsor under paragraph (c)(2)(i) of this section shall consist of the sponsor obtaining from the principal investigator an acknowledgment of the principal investigator's responsibilities under this part as responsible party, and the principal investigator acknowledging the designation as responsible party to the Director in the format specified at *https://prsinfo.clinicaltrials.gov.*

(3) *Withdrawal of the designation of a principal investigator as the responsible party.*

In the event that a principal investigator who has been designated the responsible party no longer meets or is no longer able to meet all the requirements for being so designated under paragraph (c)(2)(i) of this section, the sponsor must withdraw the designation in the format specified at *https://prsinfo.clinicaltrials.gov,* at which time the sponsor will be considered the responsible party unless and until the sponsor makes a new designation in accordance with paragraph (c)(2) of this section.

§ 11.6 What are the requirements for the submission of truthful information?

The clinical trial information submitted by a responsible party under this part shall not be false or misleading in any particular. A responsible party who submits false and/or misleading information is subject to civil monetary penalties and/or other civil or criminal remedies available under U.S. law.

§ 11.8 In what format must clinical trial information be submitted?

Information submitted under this part must be submitted electronically to ClinicalTrials.gov, in the format specified at *https://prsinfo.clinicaltrials.gov.*

§ 11.10 What definitions apply to this part?

(a) The following definitions apply to terms used in this part:

Adverse event means any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. See also the definition of ''serious adverse event.''

Applicable clinical trial means an applicable device clinical trial or an applicable drug clinical trial. Expanded access use under section 561 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bbb) is not an applicable clinical trial.

Applicable device clinical trial means:

(1) A prospective clinical study of health outcomes comparing an intervention with a device product subject to section 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360(k), 21 U.S.C. 360e, 21 U.S.C. 360j(m)) against a control in human subjects (other than a small clinical trial to determine the feasibility of a device product, or a clinical trial to test prototype device products where the primary outcome measure relates to feasibility and not to health outcomes);

(2) A pediatric postmarket surveillance of a device product as required under section 522 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 3601); or

(3) A clinical trial of a combination product with a device primary mode of action under 21 CFR part 3, provided that it meets all other criteria of the definition under this part.

Applicable drug clinical trial means a controlled clinical investigation, other than a phase 1 clinical investigation, of a drug product subject to section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) or a biological product subject to section 351 of the Public Health Service Act (42 U.S.C. 262), where ''clinical investigation'' has the meaning given in 21 CFR 312.3 and ''phase 1'' has the meaning given in 21 CFR 312.21. A clinical trial of a combination product with a drug primary mode of action under 21 CFR part 3 is also an applicable drug clinical trial, provided that it meets all other criteria of the definition under this part.

Approved drug means a drug product that is approved for any use under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) or a biological product licensed for any use under section 351 of the Public Health Service Act (42 U.S.C. 262).

Approved or cleared device means a device product that is cleared for any use under section 510(k) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C 360(k)) or approved for any use under sections 515 or 520(m) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C 360e, 360j(m)).

Arm means a pre-specified group or subgroup of human subject(s) in a clinical trial assigned to receive specific intervention(s) (or no intervention) according to a protocol.

Clinical study means research according to a protocol involving one or more human subjects to evaluate biomedical or health-related outcomes, including interventional studies and observational studies.

Clinical trial means a clinical investigation or a clinical study in which human subject(s) are prospectively assigned, according to a protocol, to one or more interventions (or no intervention) to evaluate the effect(s) of the intervention(s) on biomedical or health-related outcomes.

Clinical trial information means the data elements, including clinical trial registration information and clinical trial results information, that the responsible party is required to submit to *ClinicalTrials.gov*, as specified in section 402(j) of the Public Health

Service Act (42 U.S.C. 282(j)) and this part.

Clinical trial registration information means the data elements that the responsible party is required to submit to *ClinicalTrials.gov*, as specified in section 402(j)(2)(A)(ii) of the Public Health Service Act (42 U.S.C. 282(j)(2)(A)(ii)) or § 11.28, as applicable.

Clinical trial results information means the data elements that the responsible party is required to submit to *ClinicalTrials.gov,* as specified in sections 402(j)(3)(C) and 402(j)(3)(I) of the Public Health Service Act (42 U.S.C. 282(j)(3)(C) and (I)) or § 11.48, as applicable. If a responsible party submits clinical trial results information voluntarily for a clinical trial, clinical trial results information also means § 11.60(b)(2)(i)(B) or § 11.60(c)(2)(i)(B), as applicable.

Comparison group means a grouping of human subjects in a clinical trial that is or may be used in analyzing the results data collected during the clinical trial.

Completion date means, for a clinical trial, including an applicable clinical trial, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated. In the case of clinical trials with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes. For a pediatric postmarket surveillance of a device product that is not a clinical trial, completion date means the date on which the final report of the pediatric postmarket surveillance of the device product is submitted to FDA. For purposes of this part, completion date is referred to as ''primary completion date.''

Control or controlled means, with respect to a clinical trial, that data collected on human subjects in the clinical trial will be compared to concurrently collected data or to non-concurrently collected data (*e.g.,* historical controls, including a human subject's own baseline data), as reflected in the pre-specified primary or secondary outcome measures. For purposes of this part, all clinical trials with one or more arms and pre-specified outcome measure(s) are controlled.

Device means a device as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(h)).

Director means the NIH Director or any official of NIH to whom the NIH Director delegates authorities granted in section 402(j) of the Public Health Service Act (42 U.S.C. 282(j)).

Drug means a drug as defined in section 201(g) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(g)) or a biological product as defined in section 351 of the Public Health Service Act (42 U.S.C. 262).

Enroll or enrolled means a human subject's, or their legally authorized representative's, agreement to participate in a clinical trial following completion of the informed consent process, as required in 21 CFR part 50 and/or 45 CFR part 46, as applicable. For the purposes of this part, potential subjects who are screened for the purpose of determining eligibility for a trial, but do not participate in the trial, are not considered enrolled, unless otherwise specified by the protocol.

Human subjects protection review board means an institutional review board (IRB) as defined in 21 CFR 50.3 or 45 CFR 46.102, as applicable, that is responsible for assuring the protection of the rights, safety, and well-being of human subjects involved in a clinical trial and is adequately constituted to provide assurance of that protection. An IRB may also be known as an ''independent ethics committee.''

Interventional means, with respect to a clinical study or a clinical investigation, that participants are assigned prospectively to an intervention or interventions according to a protocol to evaluate the effect of the intervention(s) on biomedical or other health-related outcomes.

Investigational Device Exemption (IDE) has the meaning given in 21 CFR part 812.

Investigational New Drug Application (IND) has the meaning given in 21 CFR 312.3.

NCT number means the unique identification code assigned to each record in *ClinicalTrials.gov,* including a record for an applicable clinical trial, a clinical trial, or an expanded access program.

Ongoing means, with respect to a clinical trial of a drug product (including a biological product) or a device product and to a date, that one or more human subjects is enrolled in the clinical trial, and the date is before the primary completion date of the clinical trial. With respect to a pediatric postmarket surveillance of a device product, ongoing means a date between the date on which FDA approves the plan for conducting the surveillance and the date on which the final report is submitted to FDA.

Outcome measure means a pre-specified measurement that will be used to determine the effect of an experimental variable on the human subject(s) in a clinical trial. See also the definitions of ''primary outcome measure'' and ''secondary outcome measure.''

Pediatric postmarket surveillance of a device product means the active, systematic, scientifically valid collection, analysis, and interpretation of data or other information conducted under section 522 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360l) about a marketed device product that is expected to have significant use in patients who are 21 years of age or younger at the time of diagnosis or treatment. A pediatric postmarket surveillance of a device product may be, but is not always, a clinical trial.

Primary completion date means, for purposes of this part, ''completion date.'' See the definition of ''completion date.''

Primary outcome measure means the outcome measure(s) of greatest importance specified in the protocol, usually the one(s) used in the power calculation. Most clinical trials have one primary outcome measure, but a clinical trial may have more than one. For purposes of this part, ''primary outcome'' has the same meaning as primary outcome measure.

Principal investigator means the individual who is responsible for the overall scientific and technical direction of the study.

Protocol means the written description of the clinical trial, including objective(s), design, and methods. It may also include relevant scientific background and statistical considerations.

Responsible party means, with respect to a clinical trial, the sponsor of the clinical trial, as defined in 21 CFR 50.3; or the principal investigator of such clinical trial if so designated by a sponsor, grantee, contractor, or awardee, so long as the principal investigator is responsible for conducting the trial, has access to and control over the data from the clinical trial, has the right to publish the results of the trial, and has the ability to meet all of the requirements under this part for the submission of clinical trial information. For a pediatric postmarket surveillance of a device product that is not a clinical trial, the responsible party is the entity who FDA orders to conduct the pediatric postmarket surveillance of the device product.

Secondary outcome measure means an outcome measure that is of lesser importance than a primary outcome measure, but is part of a pre-specified analysis plan for evaluating the effects

of the intervention or interventions under investigation in a clinical trial and is not specified as an exploratory or other measure. A clinical trial may have more than one secondary outcome measure. For purposes of this part, ''secondary outcome'' has the same meaning as secondary outcome measure.

Secretary means the Secretary of Health and Human Services or any other official(s) to whom the Secretary delegates the authority contained in section 402(j) of the Public Health Service Act (42 U.S.C. 282(j)).

Serious adverse event means an adverse event that results in any of the following outcomes: Death, a life-threatening adverse event as defined in 21 CFR 312.32, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the human subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of a substance use disorder.

Sponsor means either a ''sponsor'' or ''sponsor-investigator,'' as each is defined in 21 CFR 50.3.

Study completion date means, for a clinical trial, the date the final subject was examined or received an intervention for purposes of final collection of data for the primary and secondary outcome measures and adverse events (*e.g.,* last subject's last visit), whether the clinical trial concluded according to the pre-specified protocol or was terminated.

U.S. FDA-regulated device product means, for purposes of this part, a device product subject to section 510(k), 515, 520(m), or 522 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360(k), 21 U.S.C. 360e, 21 U.S.C. 360j(m), 21 U.S.C. 360l).

U.S. FDA-regulated drug product means, for purposes of this part, a drug product subject to section 505 of the Federal Food, Drug, and Cosmetic Act or a biological product subject to section 351 of the Public Health Service Act (21 U.S.C. 355, 42 U.S.C. 262) .

(b) The following definitions apply to data elements of clinical trial information referenced in this part, unless otherwise specified:

(1) *Brief Title* means a short title of the clinical trial written in language intended for the lay public, including any acronym or abbreviation used publicly to identify the clinical trial.

(2) *Official Title* means the title of the clinical trial, corresponding to the title of the protocol.

(3) *Brief Summary* means a short description of the clinical trial, including a brief statement of the clinical trial's hypothesis, written in language intended for the lay public.

(4) *Primary Purpose* means the main objective of the intervention(s) being evaluated by the clinical trial.

(5) *Study Design* means a description of the manner in which the clinical trial will be conducted, including the following information:

(i) *Interventional Study Model.* The strategy for assigning interventions to human subjects.

(ii) *Number of Arms.* The number of arms in the clinical trial. For a trial with multiple periods or phases that have different numbers of arms, it means the maximum number of arms during all periods or phases.

(iii) *Arm Information.* A description of each arm of the clinical trial that indicates its role in the clinical trial, provides an informative title, and, if necessary, additional descriptive information (including which interventions are administered in each arm) to differentiate each arm from other arms in the clinical trial.

(iv) *Allocation.* The method by which human subjects are assigned to arms in a clinical trial.

(v) *Masking.* The party or parties, if any, involved in the clinical trial who are prevented from having knowledge of the interventions assigned to individual human subjects.

(6) *Study Phase* means, for a clinical trial of a drug product (including a biological product), the numerical phase of such clinical trial, consistent with terminology in 21 CFR 312.21, such as phase 2 or phase 3, and in 21 CFR 312.85 for phase 4 studies.

(7) *Study Type* means the nature of the investigation or investigational use for which clinical trial information is being submitted, *e.g.,* interventional, observational.

(8) *Pediatric Postmarket Surveillance of a Device Product* means a clinical trial or study that includes a U.S. FDA-regulated device product as an intervention and is a pediatric postmarket surveillance of a device product ordered under section 522 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 369l).

(9) *Primary Disease or Condition Being Studied in the Trial, or the Focus of the Study* means the name(s) of the disease(s) or condition(s) studied in the clinical trial, or the focus of the clinical trial. Use, if available, appropriate descriptors from NLM's Medical Subject Headings (MeSH)-controlled vocabulary thesaurus or terms from another vocabulary, such as the Systematized Nomenclature of Medicine—Clinical Terms (SNOMED CT), that has been mapped to MeSH within the Unified Medical Language System (UMLS) Metathesaurus.

(10) *Intervention Name(s)* means a brief descriptive name used to refer to the intervention(s) studied in each arm of the clinical trial. A non-proprietary name of the intervention must be used, if available. If a non-proprietary name is not available, a brief descriptive name or identifier must be used.

(11) *Other Intervention Name(s)* means other current and former name(s) or alias(es), if any, different from the Intervention Name(s), that the sponsor has used publicly to identify the intervention(s), including, but not limited to, past or present names such as brand name(s), or serial numbers.

(12) *Intervention Description* means details that can be made public about the intervention, other than the Intervention Name(s) and Other Intervention Name(s), sufficient to distinguish the intervention from other, similar interventions studied in the same or another clinical trial. For example, interventions involving drugs may include dosage form, dosage, frequency, and duration.

(13) *Intervention Type* means, for each intervention studied in the clinical trial, the general type of intervention, *e.g.,* drug, biological/vaccine, or, device.

(14) *Device Product Not Approved or Cleared by U.S. FDA* means that at least one device product studied in the clinical trial has not been previously approved or cleared by FDA for one or more uses.

(15) *Product Manufactured in and Exported from the U.S.* means that any drug product (including a biological product) or device product studied in the clinical trial is manufactured in the United States or one of its territories and exported for study in a clinical trial in another country.

(16) *Study Start Date* means the estimated date on which the clinical trial will be open for recruitment of human subjects, or the actual date on which the first human subject was enrolled.

(17) *Primary Completion Date* means the estimated or actual primary completion date. If an estimated primary completion date is used, the responsible party must update the Primary Completion Date data element once the clinical trial has reached the primary completion date to reflect the actual primary completion date.

(18) *Enrollment* means the estimated total number of human subjects to be enrolled (target number) or the actual total number of human subjects that are enrolled in the clinical trial. Once the trial has reached the primary completion date, the responsible party must update the Enrollment data element to reflect the actual number of human subjects enrolled in the clinical trial.

(19) *Primary Outcome Measure Information* means a description of each primary outcome measure, to include the following information:

(i) Name of the specific primary outcome measure;

(ii) Description of the metric used to characterize the specific primary outcome measure; and

(iii) Time point(s) at which the measurement is assessed for the specific metric used.

(20) *Secondary Outcome Measure Information* means a description of each secondary outcome measure, to include the following information:

(i) Name of the specific secondary outcome measure;

(ii) Description of the metric used to characterize the specific secondary outcome measure; and

(iii) Time point(s) at which the measurement is assessed for the specific metric used.

(21) *Eligibility Criteria* means a limited list of criteria for selection of human subjects to participate in the clinical trial, provided in terms of inclusion and exclusion criteria and suitable for assisting potential human subjects in identifying clinical trials of interest.

(22) *Sex/Gender* means the sex and, if applicable, gender of the human subjects who may participate in the clinical trial.

(23) *Age Limits* means the minimum and maximum age of human subjects who may participate in the clinical trial, provided in relevant units of time.

(24) *Accepts Healthy Volunteers* means that human subjects who do not have a disease or condition, or related conditions or symptoms, under study in the clinical trial are permitted to participate in the clinical trial.

(25) *Overall Recruitment Status* means the recruitment status for the clinical trial as a whole, based on the status of the individual sites. If at least one facility in a multi-site clinical trial has an individual site status of ''recruiting,'' then the overall recruitment status for the trial must be ''recruiting.''

(26) *Why Study Stopped* means, for a clinical trial that is suspended or terminated or withdrawn prior to its planned completion as anticipated by the protocol, a brief explanation of the reason(s) why the clinical trial was stopped.

(27) *Individual Site Status* means the recruitment status of each participating facility in a clinical trial.

(28) *Availability of Expanded Access* means, for an applicable drug clinical trial of a drug product (including a biological product) that is not an approved drug product (including a biological product), and for which the responsible party is both the manufacturer of the drug product (including a biological product) and the sponsor of the applicable clinical trial:

(i) An indication of whether there is expanded access to the investigational drug product (including a biological product) under section 561 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bbb) for those individuals who do not qualify for enrollment in the applicable clinical trial, under one or more of the following types of expanded access programs: for individual patients, including for emergency use, as specified in 21 CFR 312.310; for intermediate-size patient populations, as specified in 21 CFR 312.315; or under a treatment IND or treatment protocol, as specified in 21 CFR 312.320; and

(ii) If expanded access is available under section 561 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bbb), the NCT number of the expanded access record.

(29) *Name of the Sponsor* means the name of the entity or individual who is the sponsor of the clinical trial, as defined in this part.

(30) *Responsible Party, by Official Title* means an:

(i) Indication of whether the responsible party is the sponsor of the clinical trial, as that term is defined in 21 CFR 50.3; the sponsor-investigator, as that term is defined in 21 CFR 50.3; or a principal investigator designated pursuant to this part; and

(ii) Either:

(A) The official name of the entity, if the responsible party is an entity; or

(B) The official title and primary organizational affiliation of the individual, if the responsible party is an individual.

(31) *Facility Information* means, for each participating facility in a clinical trial, the following information:

(i) Facility Name, meaning the full name of the organization where the clinical trial is being conducted;

(ii) Facility Location, including city, state, country and zip code for U.S. locations (including territories of the United States) and city and country for locations in other countries; and

(iii) Either:

(A) For each facility participating in a clinical trial, Facility Contact, including the name or title, telephone number, and email address of a person to whom questions concerning the trial and enrollment at that site can be addressed; or

(B) Central Contact Person, including the name or title, toll-free telephone number, and email address of a person to whom questions concerning enrollment at any location of the trial can be addressed.

(32) *Unique Protocol Identification Number* means any unique identifier assigned to the protocol by the sponsor.

(33) *Secondary ID* means:

(i) Any identifier(s) other than the organization's unique protocol identifier or NCT number that is assigned to the clinical trial, including any unique clinical trial identifiers assigned by other publicly available clinical trial registries. If the clinical trial is funded in whole or in part by a U.S. Federal Government agency, the complete grant or contract number must be submitted as a Secondary ID.

(ii) A description of the type of Secondary ID.

(34) *U.S. Food and Drug Administration IND or IDE Number* means an indication of whether there is an IND or IDE for the clinical trial and, if so, each of the following elements:

(i) Name or abbreviation of the FDA center with whom the IND or IDE is filed;

(ii) IND or IDE number assigned by the FDA center; and

(iii) For an IND, the IND serial number, as defined in 21 CFR 312.23(e), if any, assigned to the clinical trial.

(35) *Human Subjects Protection Review Board Status* means information to indicate whether a clinical trial has been reviewed and approved by a human subjects protection review board or whether such review is not required per applicable law (*e.g.,* 21 CFR part 56, 45 CFR part 46, or other applicable regulation). Human Subjects Protection Review Board Status must be listed as ''approved'' if at least one human subjects protection review board has approved the clinical trial.

(36) *Record Verification Date* means the date on which the responsible party last verified the clinical trial information in the entire ClinicalTrials.gov record for the clinical trial, even if no additional or updated information was submitted at that time.

(37) *Responsible Party Contact Information* means administrative information to identify and allow communication with the responsible party by telephone, email, and regular mail or delivery service. Responsible Party Contact Information includes the name, official title, organizational affiliation, physical address, mailing address, phone number, and email address of the individual who is the responsible party or of a designated employee of the organization that is the responsible party.

(38) *Studies a U.S. FDA-regulated Device Product* means that a clinical trial studies a device product subject to section 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360(k), 21 U.S.C. 360e, 21 U.S.C. 360j(m)).

(39) *Studies a U.S. FDA-regulated Drug Product* means a clinical trial studies a drug product (including a biological product) subject to section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) or section 351 of the Public Health Service Act (42 U.S.C. 262).

(40) *Post Prior to U.S. FDA Approval or Clearance* means, for an applicable device clinical trial of a device product that has not been previously approved or cleared, the responsible party indicates to the Director that it is authorizing the Director, in accordance with § 11.35(b)(2)(ii), to publicly post its clinical trial registration information, which would otherwise be subject to delayed posting, as specified in § 11.35(b)(2)(i), prior to the date of FDA approval or clearance of its device product.

(41) *Study Completion Date* means the estimated or actual study completion date. Once the clinical trial has reached the study completion date, the responsible party must update the Study Completion Date data element to reflect the actual study completion date in accordance with § 11.64(a)(1)(ii)(J) .

Subpart B—Registration

§ 11.20 Who must submit clinical trial registration information?

The responsible party for an applicable clinical trial specified in § 11.22 must submit clinical trial registration information for that clinical trial.

§ 11.22 Which applicable clinical trials must be registered?

(a) *General specification.* (1) Any applicable clinical trial that is initiated after September 27, 2007, must be registered.

(2) Any applicable clinical trial that is initiated on or before September 27, 2007, and is ongoing on December 26, 2007, must be registered.

(3) *Determining the date of initiation for an applicable clinical trial.* An applicable clinical trial, other than a pediatric postmarket surveillance of a device product that is not a clinical trial, is considered to be initiated on the date on which the first human subject is enrolled. A pediatric postmarket surveillance of a device product that is not a clinical trial is considered to be initiated on the date on which FDA approves the plan for conducting the surveillance.

(b) *Determination of applicable clinical trial for a clinical trial or study initiated on or after January 18, 2017.* A clinical trial or study that, at any point in time, meets the conditions listed in paragraph (b)(1) or (2) of this section will be considered to meet the definition of an applicable clinical trial.

(1) *Applicable device clinical trial.* A clinical trial or study that meets the conditions listed in either paragraph (b)(1)(i) or (ii) of this section is an applicable device clinical trial:

(i) The study is a pediatric postmarket surveillance of a device product as required by FDA under section 522 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 3601).

(ii) The study is a clinical trial with one or more arms that meets all of the following criteria:

(A) Study Type is interventional;

(B) Primary Purpose of the clinical trial is other than a feasibility study;

(C) The clinical trial Studies a U.S. FDA-regulated Device Product; and

(D) One or more of the following applies:

(*1*) At least one Facility Location is within the United States or one of its territories,

(*2*) A device product under investigation is a Product Manufactured in and Exported from the U.S. or one of its territories for study in another country, or

(*3*) The clinical trial has a U.S. Food and Drug Administration IDE Number.

(2) *Applicable drug clinical trial.* A clinical trial with one or more arms that meets the following conditions is an applicable drug clinical trial:

(i) Study Type is interventional;

(ii) Study Phase is other than phase 1;

(iii) The clinical trial Studies a U.S. FDA-regulated Drug Product; and

(iv) One or more of the following applies:

(A) At least one Facility Location for the clinical trial is within the United States or one of its territories,

(B) A drug product (including a biological product) under investigation is a Product Manufactured in and Exported from the U.S. or one of its territories for study in another country, or

(C) The clinical trial has a U.S. Food and Drug Administration IND Number.

§ 11.24 When must clinical trial registration information be submitted?

(a) *General.* Except as provided in paragraph (b) of this section, the responsible party for an applicable clinical trial for which submission of clinical trial registration information is required must submit the clinical trial registration information specified in section 402(j)(2)(A)(ii) of the Public Health Service Act (42 U.S.C. 282(j)(2)(A)(ii)) or § 11.28(a), as applicable, not later than December 26, 2007, or 21 calendar days after the first human subject is enrolled, whichever date is later.

(b) *Exceptions:.* (1) The responsible party for an applicable clinical trial that is a clinical trial and for which the submission of clinical trial registration information is required and that is not for a serious or life-threatening disease or condition must submit clinical trial registration information as specified in section 402(j)(2)(A)(ii) of the Public Health Service Act (42 U.S.C. 282(j)(2)(A)(ii)) or § 11.28(a), as applicable, not later than September 27, 2008, or 21 calendar days after the first human subject is enrolled, whichever date is later.

(2) The responsible party for an applicable device clinical trial that is a pediatric postmarket surveillance of a device product and is not a clinical trial must submit clinical trial registration information, as specified in section 402(j)(2)(A)(ii) of the Public Health Service Act (42 U.S.C. 282(j)(2)(A)(ii)) or § 11.28(b), not later than December 26, 2007, or 21 calendar days after FDA approves the postmarket surveillance plan, whichever date is later.

§ 11.28 What constitutes clinical trial registration information?

(a) For each applicable clinical trial that must be registered with ClinicalTrials.gov, other than a pediatric postmarket surveillance of a device product that is not a clinical trial, the responsible party must submit the following information:

(1) For such applicable clinical trials that were initiated before January 18,

2017, the responsible party must submit the information specified in section 402(j)(2)(A)(ii) of the Public Health Service Act (42 U.S.C. 282(j)(2)(A)(ii)).

(2) For such applicable clinical trials that are initiated on or after January 18, 2017, the responsible party must submit the data elements listed below:

(i) Descriptive information:

(A) Brief Title;

(B) Official Title;

(C) Brief Summary;

(D) Primary Purpose;

(E) Study Design;

(F) Study Phase, for an applicable drug clinical trial;

(G) Study Type;

(H) Pediatric Postmarket Surveillance of a Device Product, for an applicable device clinical trial that is a Pediatric Postmarket Surveillance of a Device Product;

(I) Primary Disease or Condition Being Studied in the Trial, or the Focus of the Study;

(J) Intervention Name(s), for each intervention studied;

(K) Other Intervention Name(s), for each intervention studied;

(L) Intervention Description, for each intervention studied;

(M) Intervention Type, for each intervention studied;

(N) Studies a U.S. FDA-regulated Device Product;

(O) Studies a U.S. FDA-regulated Drug Product;

(P) Device Product Not Approved or Cleared by U.S. FDA, if any studied intervention is a device product;

(Q) Post Prior to U.S. FDA Approval or Clearance, for an applicable device clinical trial that studies at least one device product not previously approved or cleared by the U.S. FDA;

(R) Product Manufactured in and Exported from the U.S., if the entry for U.S. Food and Drug Administration IND or IDE Number in § 11.28(a)(2)(iv)(C) indicates that there is no IND or IDE for the clinical trial, and the entry(ies) for Facility Information in § 11.28(a)(2)(iii)(C) include no facility locations in the United States or its territories;

(S) Study Start Date;

(T) Primary Completion Date;

(U) Study Completion Date;

(V) Enrollment;

(W) Primary Outcome Measure Information, for each primary outcome measure; and

(X) Secondary Outcome Measure Information, for each secondary outcome measure.

(ii) Recruitment information:

(A) Eligibility Criteria;

(B) Sex/Gender;

(C) Age Limits;

(D) Accepts Healthy Volunteers;

(E) Overall Recruitment Status;

(F) Why Study Stopped;

(G) Individual Site Status; and

(H) Availability of Expanded Access. If expanded access is available for an investigational drug product (including a biological product), an expanded access record must be submitted in accordance with § 11.28(c), unless an expanded access record was submitted previously in accordance with that provision.

(iii) Location and contact information:

(A) Name of the Sponsor;

(B) Responsible Party, by Official Title; and

(C) Facility Information.

(iv) Administrative data:

(A) Unique Protocol Identification Number;

(B) Secondary ID;

(C) U.S. Food and Drug Administration IND or IDE Number;

(D) Human Subjects Protection Review Board Status;

(E) Record Verification Date; and

(F) Responsible Party Contact Information.

(b) Pediatric postmarket surveillance of a device product that is not a clinical trial. For each pediatric postmarket surveillance of a device product that is not a clinical trial, the responsible party must submit the following information:

(1) For such applicable device clinical trials that were initiated before January 18, 2017, the responsible party must submit the information specified in section 402(j)(2)(A)(ii) of the Public Health Service Act (42 U.S.C. 282(j)(2)(A)(ii)).

(2) For such applicable device clinical trials that are initiated on or after January 18, 2017, the responsible party must submit the data elements listed below:

(i) Descriptive information:

(A) *Brief Title.* A short title of the pediatric postmarket surveillance of a device product in language intended for the lay public. If an acronym or abbreviation is used to publicly identify the surveillance, it must be provided.

(B) *Official Title.* The title of the pediatric postmarket surveillance of a device product, corresponding to the title of the protocol or the FDA-approved plan for conducting the surveillance

(C) *Brief Summary.* A short description of the pediatric postmarket surveillance of a device product, including a brief statement of the hypothesis or objective, written in language intended for the lay public, and a general description of the surveillance design, including relevant population information

(D) *Study Type.* The type of study being registered. In the case of a pediatric postmarket surveillance of a device product that is not a clinical trial, a study type of ''observational'' is required.

(E) *Pediatric Postmarket Surveillance of a Device Product.* For a study that includes an FDA-regulated device product as an intervention and is a pediatric postmarket surveillance of a device product

(F) *Primary Disease or Condition Being Studied, or the Focus of the Study.* The name(s) of the disease(s) or condition(s) being studied in the pediatric postmarket surveillance of a device product, or the focus of the surveillance study. Use, if available, appropriate descriptors fromNLM's MeSH-controlled vocabulary thesaurus or terms from another vocabulary, such as the SNOMED CT, that has been mapped to MeSH within the UMLS Metathesaurus.

(G) *Intervention Name(s).* A brief descriptive name used to refer to each intervention studied in the pediatric postmarket surveillance of a device product. A non-proprietary name of the intervention must be used, if available. If a non-proprietary name is not available, a brief descriptive name or identifier must be used.

(H) *Other Intervention Name(s).* Any other current and former name(s) or alias(es), different from the Intervention Name(s), that the sponsor has used publicly to identify the intervention(s), including, but not limited to, past or present names such as brand name(s), or serial numbers

(I) *Intervention Description.* Details that can be made public about each intervention, other than the Intervention Name(s) and Other Intervention Name(s), sufficient to distinguish the intervention from other, similar interventions studied in the same or another clinical trial or pediatric postmarket surveillance of a device product that is not a clinical trial

(J) *Intervention Type.* For each intervention studied in the pediatric postmarket surveillance of a device product, the general type of intervention

(K) *Study Start Date.* The date on which FDA approves the pediatric postmarket surveillance plan, as specified in 21 CFR 822.19(a).

(L) *Primary Completion Date.* The estimated or actual date on which the final report of the pediatric postmarket surveillance of a device product is expected to be submitted to FDA. Once the final report has been submitted, this is the actual date on which the final report is submitted to FDA.

(ii) Location and contact information:

(A) Name of the Sponsor.

(B) Responsible Party, by Official Title:

(*1*) If the responsible party is an entity, the official name of the entity; or

(*2*) If the responsible party is an individual, the official title and primary organizational affiliation of the individual.

(C) *Contact Information.* The name or official title, toll-free telephone number, and email address of a person to whom questions concerning the pediatric postmarket surveillance of a device product can be addressed.

(iii) Administrative data:

(A) *Unique Protocol Identification Number.* The unique identifier assigned to the pediatric postmarket surveillance of a device product by the sponsor, if any.

(B) *Secondary ID:* (*1*) Identifier(s) other than the organization's unique protocol identifier or NCT number that is assigned to the pediatric postmarket surveillance of a device product, if any, including any unique identifiers assigned by other publicly available clinical study registries. If the pediatric postmarket surveillance of a device product is funded in whole or in part by a U.S. Federal Government agency, the complete grant or contract number must be submitted as a Secondary ID.

(*2*) For each secondary ID listed, a description of the type of secondary ID.

(C) *Human Subjects Protection Review Board Status.* Information to indicate whether a pediatric postmarket surveillance of a device product has been reviewed and approved by a human subjects protection review board or whether such review is not required per applicable law (*e.g.,* 21 CFR part 56, 45 CFR part 46, or other applicable regulation). Human Subjects Protection Review Board Status must be listed as ''approved'' if at least one human subjects protection review board has approved the pediatric postmarket surveillance.

(D) *Record Verification Date.* The date on which the responsible party last verified the clinical trial information in the entire ClinicalTrials.gov record for the pediatric postmarket surveillance of a device product, even if no additional or updated information was submitted at that time

(E) *Responsible Party Contact Information.* Administrative information sufficient to identify and allow communication with the responsible party by telephone, email, and regular mail or delivery service. Responsible Party Contact Information includes the name, official title, organizational affiliation, physical address, mailing address, phone number, and email address of the individual who is the responsible party or of a designated employee of the organization that is the responsible party.

(c) *Expanded access record.* If expanded access is available, as specified in 21 CFR 312.315 (for an intermediate-size patient population) or 21 CFR 312.320 (under a treatment IND or treatment protocol), for an investigational drug product (including a biological product) studied in an applicable drug clinical trial, and the data elements set forth in paragraphs (c)(1) through (4) of this section have not been submitted in an expanded access record for that investigational product, the responsible party, if both the manufacturer of the investigational product and the sponsor of the applicable clinical trial, must submit the clinical trial information specified in paragraphs (c)(1) through (4) of this section to ClinicalTrials.gov in the form of an expanded access record. If expanded access is available only as specified in 21 CFR 312.310 (for individual patients, including for emergency use) for an investigational drug product (including a biological product) studied in an applicable drug clinical trial, and the data elements set forth in paragraphs (c)(1)(i), (iii), (iv), (vi), (ix), (x), (c)(2)(iv), (c)(3), (c)(4)(i), (iii),(iv), and (v) of this section have not been submitted in an expanded access record for that investigational product, the responsible party, if both the manufacturer of the investigational product and the sponsor of the applicable clinical trial, must submit the clinical trial information specified in those paragraphs to ClinicalTrials.gov in the form of an expanded access record.

(1) Descriptive information:

(i) *Brief Title.* A short title identifying the expanded access, written in language intended for the lay public. If an acronym or abbreviation is used publicly to identify the expanded access, it must be provided.

(ii) *Official Title.* The title, if any, of the expanded access program corresponding to the title that has been submitted to FDA for that program

(iii) *Brief Summary.* A short description of the availability of expanded access, including the procedure for requesting the investigational drug product (including a biological product).

(iv) *Study Type.* The nature of the investigation or investigational use for which clinical trial information is being submitted, *i.e.,* ''expanded access''.

(v) *Primary Disease or Condition.* The name(s) of the disease(s) or condition(s) for which expanded access to the investigational drug product (including a biological product) is available. Use, if available, appropriate descriptors from NLM's MeSH-controlled vocabulary thesaurus, or terms from another vocabulary, such as the SNOMED CT, that has been mapped to MeSH within the UMLS Metathesaurus.

(vi) *Intervention Name(s).* A brief descriptive name used to refer to the investigational drug product (including a biological product) that is available through expanded access. A non-proprietary name of the intervention must be used, if available. If a non-proprietary name is not available, a brief descriptive name or identifier must be used.

(vii) *Other Intervention Name(s).* Any other current and former name(s) or alias(es), different from the Intervention Name(s), that the sponsor has used publicly to identify the intervention, including, but not limited to, past or present names such as brand name(s), or serial numbers.

(viii) *Intervention Description.* Details that can be made public about each intervention, other than the Intervention Name(s) or Other Intervention Name(s), sufficient to distinguish the intervention from other, similar interventions that are available through expanded access or in clinical trials.

(ix) *Intervention Type.* For each investigational drug product (including a biological product) for which expanded access is available, the general type of intervention, *e.g.,* drug.

(x) *Expanded Access Type.* The type(s) of expanded access for which the investigational drug product (including a biological product) is available, as specified in § 11.10(b)(28).

(2) Recruitment information:

(i) *Eligibility Criteria.* A limited list of criteria for determining who is eligible to receive the investigational drug product (including a biological product) through expanded access, provided in terms of inclusion and exclusion criteria and suitable for assisting potential patients in identifying investigational drug products (including biological products) of interest for which expanded access is available.

(ii) *Sex/Gender.* The sex and gender (if applicable) of the patients for whom expanded access is available.

(iii) *Age Limits.* The minimum and maximum age of patients for whom expanded access is available, provided in relevant units of time.

(iv) *Expanded Access Status.* The status of availability of the investigational drug product (including a biological product) through expanded access.

(3) Contact information:

(i) *Name of the Sponsor.*

(ii) *Responsible Party, by Official Title.* The official name of the entity.

(iii) *Contact Information.* The name or official title, toll-free telephone number, and email address of a person to whom questions concerning expanded access can be addressed.

(4) Administrative data:

(i) *Unique Protocol Identification Number.* Any unique identifier assigned by the sponsor to refer to the availability of its investigational drug product (including a biological product) for expanded access use or to identify the expanded access record.

(ii) *Secondary ID:* (A) Any identifier(s) other than the Unique Protocol Identification Number or the NCT number that is assigned to the expanded access record, including any unique identifiers assigned by other publicly available clinical trial or expanded access registries.

(B) For each Secondary ID listed, a description of the type of Secondary ID.

(iii) *U.S. Food and Drug Administration IND Number.* An indication of whether there is an IND and, if so, each of the following elements:

(A) Name or abbreviation of the FDA center with whom the IND is filed (*i.e.,* CDER or CBER), if applicable;

(B) IND number (assigned by the FDA center) under which the investigational drug product (including a biological product) is being made available for expanded access, if applicable; and

(C) IND serial number. as defined in 21 CFR 312.23(e), if any, assigned to the expanded access.

(iv) *Record Verification Date.* The date on which the responsible party last verified the information in the expanded access record, even if no additional or updated information was submitted at that time.

(v) *Responsible Party Contact Information.* Administrative information sufficient to identify and allow communication with the responsible party entering the clinical trial information into the expanded access record by telephone, email, and regular mail or delivery service. Responsible Party Contact Information includes the name, official title, organizational affiliation, physical address, mailing address, phone number, and email address of the individual who is the responsible party or of a designated employee of the organization that is the responsible party.

§ 11.35 By when will the NIH Director post clinical trial registration information submitted under § 11.28?

(a) *Applicable drug clinical trial.* The Director will post publicly on *ClinicalTrials.gov* the clinical trial registration information, except for certain administrative data, for an applicable drug clinical trial not later than 30 calendar days after the responsible party has submitted such information, as specified in § 11.24.

(b) *Applicable device clinical trial.* (1) For an applicable device clinical trial of a device product that was previously approved or cleared, the Director will post publicly on *ClinicalTrials.gov* the clinical trial registration information, except for certain administrative data, as soon as practicable, but not later than 30 calendar days after clinical trial results information is required to be posted, as specified in § 11.52.

(2) For an applicable device clinical trial of a device product that has not been previously approved or cleared:

(i) The Director will post publicly on *ClinicalTrials.gov* the clinical trial registration information, except for certain administrative data, not earlier than the date of FDA approval or clearance of the device product and not later than 30 calendar days after the date of such approval or clearance, except as otherwise provided in paragraph (b)(2)(ii) of this section.

(ii) If, prior to the date of approval or clearance of the device product, the responsible party for an applicable clinical trial that is initiated on or after January 18, 2017, indicates to the Director, by submitting the Post Prior to U.S. FDA Approval or Clearance data element under § 11.28(a)(2)(i)(Q), that it is authorizing the Director to publicly post its clinical trial registration information, which would otherwise be subject to delayed posting as specified in paragraph (b)(2)(i) of this section, prior to the date of FDA approval or clearance of its device product, the Director will publicly post the registration information, except for certain administrative data, as soon as practicable.

Subpart C—Results Information Submission

§ 11.40 Who must submit clinical trial results information?

The responsible party for an applicable clinical trial specified in § 11.42 must submit clinical trial results information for that clinical trial.

§ 11.42 For which applicable clinical trials must clinical trial results information be submitted?

(a) *Applicable clinical trials for which the studied product is approved, licensed, or cleared by FDA.* Unless a waiver of the requirement to submit clinical trial results information is granted in accordance with § 11.54, clinical trial results information must be submitted for any applicable clinical trial for which the studied product is approved, licensed, or cleared by FDA for which submission of clinical trial registration information is required in accordance with the following:

(1) If the primary completion date is before January 18, 2017, the responsible party must submit the clinical trial results information specified in sections 402(j)(3)(C) and 402(j)(3)(I) of the Public Health Service Act (42 U.S.C. 282(j)(3)(C) and 42 U.S.C. 282(j)(3)(I)); or

(2) If the primary completion date is on or after January 18, 2017, the responsible party must submit the clinical trial results information specified in § 11.48.

(b) *Applicable clinical trials for which the studied product is not approved, licensed, or cleared by FDA.* Unless a waiver of the requirement to submit clinical trial results information is granted in accordance with § 11.54, clinical trial results information specified in § 11.48 must be submitted for any applicable clinical trial with a primary completion date on or after January 18, 2017 for which clinical trial registration information is required to be submitted and for which the studied product is not approved, licensed, or cleared by FDA.

§ 11.44 When must clinical trial results information be submitted for applicable clinical trials subject to § 11.42?

(a) *Standard submission deadline.* In general, for applicable clinical trials subject to § 11.42, clinical trial results information specified in sections 402(j)(3)(C) and 402(j)(3)(I) of the Public Health Service Act (42 U.S.C. 282(j)(3)(C) and 42 U.S.C. 282(j)(3)(I)) or in § 11.48, as applicable, must be submitted no later than 1 year after the primary completion date of the applicable clinical trial.

(b) *Delayed submission of results information with certification if seeking approval, licensure, or clearance of a new use*—(1) *General requirements.* If, prior to the results information submission deadline specified under paragraph (a) of this section, the responsible party submits a certification that an applicable clinical trial involves an FDA-regulated drug product (including a biological product) or

device product that previously has been approved, licensed, or cleared, for which the manufacturer is the sponsor of the applicable clinical trial and for which an application or premarket notification seeking approval, licensure, or clearance of the use being studied (which is not included in the labeling of the approved, licensed, or cleared drug product (including a biological product) or device product) has been filed or will be filed within 1 year with FDA, the deadline for submitting clinical trial results information, as specified in sections 402(j)(3)(C) and 402(j)(3)(I) of the Public Health Service Act (42 U.S.C. 282(j)(3)(C) and 42 U.S.C. 282(j)(3)(I)) or § 11.48, as applicable, will be 30 calendar days after the earliest of the following events:

(i) FDA approves, licenses, or clears the drug product (including a biological product) or device product for the use studied in the applicable clinical trial;

(ii) FDA issues a letter that ends the regulatory review cycle for the application or submission but does not approve, license, or clear the drug product (including a biological product) or device product for the use studied in the applicable clinical trial; or

(iii) The application or premarket notification seeking approval, licensure, or clearance of the new use is withdrawn without resubmission for not less than 210 calendar days.

(2) *Two-year limitation.* Notwithstanding the deadlines specified in paragraph (b)(1) of this section, the responsible party must submit clinical trial results information specified in paragraph (b)(1) of this section not later than the date that is 2 years after the date that the certification was submitted, except to the extent that paragraph (d) of this section applies.

(3) *Additional requirements.* If a responsible party who is both the manufacturer of the drug product (including a biological product) or device product studied in an applicable clinical trial and the sponsor of the applicable clinical trial submits a certification in accordance with paragraph (b)(1) of this section, that responsible party must submit such a certification for each applicable clinical trial that meets the following criteria:

(i) The applicable clinical trial is required to be submitted in an application or premarket notification seeking approval, licensure, or clearance of a new use; and

(ii) The applicable clinical trial studies the same drug product (including a biological product) or device product for the same use as studied in the applicable clinical trial for which the initial certification was submitted.

(c) *Delayed submission of results with certification if seeking initial approval, licensure, or clearance.*—(1) *General requirements.* If, prior to the submission deadline specified under paragraph (a) of this section, a responsible party submits a certification that an applicable clinical trial studies an FDA-regulated drug product (including a biological product) or device product that was not approved, licensed, or cleared by FDA for any use before the primary completion date of the trial, and that the sponsor intends to continue with product development and is either seeking, or may at a future date seek, FDA approval, licensure, or clearance of the drug product (including a biological product) or device product under study, the deadline for submitting clinical trial results information, as specified in § 11.48, will be 30 calendar days after the earlier of the date on which:

(i) FDA approves, licenses, or clears the drug product (including a biological product) or device product for any use that is studied in the applicable clinical trial; or

(ii) The marketing application or premarket notification is withdrawn without resubmission for not less than 210 calendar days.

(2) *Two-year limitation.* Notwithstanding the deadlines established in paragraph (c)(1) of this section, the responsible party must submit clinical trial results information specified in paragraph (c)(1) of this section not later than 2 years after the date on which the certification was submitted, except to the extent that paragraph (d) of this section applies.

(d) *Submitting partial results information.* (1) If clinical trial results information specified in sections 402(j)(3)(C) and 402(j)(3)(I) of the Public Health Service Act (42 U.S.C. 282(j)(3)(C) and 42 U.S.C. 282(j)(3)(I)) or § 11.48, as applicable, has not been collected for a secondary outcome measure(s) or additional adverse event information by the primary completion date, the responsible party must submit the remaining required clinical trial results information for secondary outcome measure(s) or additional adverse event information for that clinical trial by the following deadlines:

(i) For secondary outcome measure(s), by the later of:

(A) One year after the date on which the final subject is examined or receives an intervention for the purposes of final collection of data for that secondary outcome measure, whether the clinical trial was concluded according to the pre-specified protocol or was terminated; or

(B) If a certification to delay results information submission has been submitted under paragraph (b) or (c) of this section, the date on which results information for the primary outcome measures is due pursuant to paragraph (b) or (c) of this section.

(ii) For additional adverse event information, by the later of:

(A) One year after the date of data collection for additional adverse event information, whether the clinical trial was concluded according to the pre-specified protocol or was terminated; or

(B) If a certification to delay results information submission has been submitted under paragraph (b) or (c) of this section, the date on which results information for the primary outcome measures is due pursuant to paragraph (b) or (c) of this section.

(2) Except, if clinical trial results information was submitted for the primary outcome measure(s) prior to the effective date of these regulations but data collection for all of the secondary outcome measure(s) or additional adverse event information is not completed until on or after January 18, 2017, clinical trial results information for all primary and secondary outcome measures and adverse event information for the clinical trial must be submitted as specified in sections 402(j)(3)(C) and 402(j)(3)(I) of the Public Health Service Act (42 U.S.C. 282(j)(3)(C) and 42 U.S.C. 282(j)(3)(I)).

(3) For each submission of partial results information for a clinical trial, as specified in paragraph (d)(1) of this section:

(i) If any amendments were made to the protocol and/or statistical analysis plan as described in § 11.48(a)(5) since the previous submission of partial results information, the responsible party must submit a copy of the revised protocol and/or statistical analysis plan; and

(ii) If information about certain agreements as described in § 11.48(a)(6)(ii) has changed since the previous submission of partial results information, the responsible party must submit information to reflect the new status of certain agreements between the principal investigator and the sponsor.

(e) *Extensions for good cause.* (1) A responsible party may request an extension of the deadline for submitting clinical trial results information subject to paragraphs (e)(1)(i) and (ii) of this section or section 402(j)(3)(E)(vi) of the Public Health Service Act (42 U.S.C. 282(j)(3)(E)(vi)), as applicable, and may request more than one extension for the same applicable clinical trial.

(i) The responsible party must submit a request for an extension to *ClinicalTrials.gov* prior to the date on which clinical trial results information would otherwise be due in accordance with paragraph (a), (b), (c), (d), (e), or (f) of this section.

(ii) A request for an extension must contain the following:

(A) Description of the reason(s) why clinical trial results information cannot be provided according to the deadline, with sufficient detail to allow for the evaluation of the request; and

(B) Estimate of the date on which the clinical trial results information will be submitted.

(2) *Decision and submission deadline.* The Director will provide a response electronically to the responsible party indicating whether the requested extension demonstrates good cause and has been granted.

(i) If the extension request is granted, the responsible party must submit clinical trial results information not later than the date of the deadline specified in the electronic response.

(ii) If the extension request is denied, the responsible party must either appeal in accordance with paragraph (e)(3) of this section or submit clinical trial results information specified in § 11.48 by the later of the submission deadline specified in paragraph (a), (b), (c), (d), (e), or (f) of this section, as applicable, or 30 calendar days after the date on which the electronic notice of the denial is sent to the responsible party.

(3) *Appealing a denied extension request.* (i) A responsible party who seeks to appeal a denied extension request or the deadline specified in a granted extension must submit an appeal to the Director in the format specified at *https://prsinfo.clinicaltrials.gov/* not later than 30 calendar days after the date on which the electronic notification of the granting or denial of the request is sent to the responsible party.

(ii) An appeal must contain an explanation of the reason(s) why the initial decision to deny the extension request or to grant the extension request with a shorter deadline than requested should be overturned or revised, with sufficient detail to allow for the evaluation of the appeal.

(iii) The Director will provide an electronic notification to the responsible party indicating whether the requested extension has been granted upon appeal.

(iv) If the Director grants the extension request upon appeal, the responsible party must submit clinical trial results information not later than the deadline specified in the electronic notification specified in paragraph (e)(3)(iii) of this section.

(v) If the Director denies the appeal of a denied extension request, the responsible party must submit clinical trial results information by the later of the deadline specified in paragraph (a), (b), (c), (d), (e), or (f) of this section, or 30 calendar days after the electronic notification of the denial of the appeal, specified in paragraph (e)(3)(iii) of this section, is sent to the responsible party.

(vi) If the Director denies an appeal of a denied deadline specified in a granted extension request, the responsible party must submit clinical trial results information by the later of the deadline specified in the notification granting the extension request, specified in paragraph (e)(2)(i) of this section, or 30 calendar days after the electronic notification denying the appeal, specified in paragraph (e)(3)(iii) of this section, is sent to the responsible party.

(f) *Pediatric postmarket surveillance of a device product that is not a clinical trial.* For each pediatric postmarket surveillance of a device product that is not a clinical trial as defined in this part, the responsible party must submit clinical trial results information as specified in § 11.48(b) or section 402(j)(C)(3) of the Public Health Service Act (42 U.S.C. 282(j)(C)(3)), as applicable, not later than 30 calendar days after the date on which the final report of the approved pediatric postmarket surveillance of a device product, as specified in 21 CFR 822.38, is submitted to FDA.

§ 11.48 What constitutes clinical trial results information?

(a) For each applicable clinical trial, other than a pediatric postmarket surveillance of a device product that is not a clinical trial, for which clinical trial results information must be submitted under § 11.42, the responsible party must provide the following:

(1) *Participant flow.* Information for completing a table documenting the progress of human subjects through a clinical trial, by arm, including the number who started and completed the clinical trial. This information must include the following elements:

(i) *Participant Flow Arm Information.* A brief description of each arm used for describing the flow of human subjects through the clinical trial, including a descriptive title used to identify each arm;

(ii) *Pre-assignment Information.* A description of significant events in the clinical trial that occur after enrollment and prior to assignment of human subjects to an arm, if any; and

(iii) *Participant Data.* The number of human subjects that started and completed the clinical trial, by arm. If assignment is based on a unit other than participants, also include a description of the unit of assignment and the number of units that started and completed the clinical trial, by arm.

(2) *Demographic and baseline characteristics.* Information for completing a table of demographic and baseline measures and data collected by arm or comparison group and for the entire population of human subjects who participated in the clinical trial. This information must include the following elements:

(i) *Baseline Characteristics Arm/Group Information.* A brief description of each arm or comparison group used for describing the demographic and baseline characteristics of the human subjects in the clinical trial, including a descriptive title used to identify each arm or comparison group.

(ii) *Baseline Analysis Population Information*—(A) *Overall Number of Baseline Participants.* The total number of human subjects for whom baseline characteristics were measured, by arm or comparison group and overall.

(B) *Overall Number of Units Analyzed.* If the analysis is based on a unit other than participants, a description of the unit of analysis and the number of units for which baseline measures were measured and analyzed, by arm or comparison group and overall.

(C) *Analysis Population Description.* If the Overall Number of Baseline Participants (or units) differs from the number of human subjects (or units) assigned to the arm or comparison group and overall, a brief description of the reason(s) for the difference.

(iii) *Baseline Measure Information.* A description of each baseline or demographic characteristic measured in the clinical trial, including age, sex/gender, race, ethnicity (if collected under the protocol), and any other measure(s) that were assessed at baseline and are used in the analysis of the primary outcome measure(s) in accordance with § 11.48(a)(3). The description of each measure must include the following elements:

(A) Name and description of the measure, including any categories that are used to submit Baseline Measure Data.

(B) *Measure Type and Measure of Dispersion:* For each baseline measure submitted, an indication of the type of data to be submitted and the associated measure of dispersion.

(C) *Unit of Measure.* For each baseline measure for which data are collected, the unit of measure.

(iv) *Baseline Measure Data.* The value(s) for each submitted baseline measure, by arm or comparison group and for the entire population of human subjects for whom baseline characteristics were measured.

(v) Number of baseline participants (and units), by arm or comparison group and overall, if different from the Overall Number of Baseline Participants or Overall Number of Units Analyzed in § 11.48(a)(2)(ii)(A) and (B), respectively.

(3) *Outcomes and statistical analyses.* Information for completing a table of data for each primary and secondary outcome measure by arm or comparison group, including the result(s) of scientifically appropriate statistical analyses that were performed on the outcome measure data, if any. This information must include the following elements:

(i) *Outcome Measure Arm/Group Information.* A brief description of each arm or comparison group used for submitting an outcome measure for the clinical trial, including a descriptive title to identify each arm or comparison group.

(ii) *Analysis Population Information*—(A) *Number of Participants Analyzed.* The number of human subjects for whom an outcome was measured and analyzed, by arm or comparison group.

(B) *Number of Units Analyzed.* If the analysis is based on a unit other than participants, a description of the unit of analysis and the number of units for which an outcome was measured and analyzed, by arm or comparison group.

(C) *Analysis Population Description.* If the Number of Participants Analyzed or Number of Units Analyzed differs from the number of human subjects or units assigned to the arm or comparison group, a brief description of the reason(s) for the difference.

(iii) *Outcome Measure Information.* A description of each outcome measure, to include the following elements:

(A) Name of the specific outcome measure, including the titles of any categories in which Outcome Measure Data in § 11.48(a)(3)(iv) are aggregated.

(B) Description of the metric used to characterize the specific outcome measure.

(C) Time point(s) at which the measurement was assessed for the specific metric.

(D) *Outcome Measure Type.* The type of outcome measure, whether primary, secondary, other pre-specified, or post-hoc.

(E) *Measure Type and Measure of Dispersion or Precision.* For each outcome measure for which data are collected, the type of data submitted and the measure of dispersion or precision.

(F) *Unit of Measure.* For each outcome measure for which data are collected, the unit of measure.

(iv) *Outcome Measure Data.* The measurement value(s) for each outcome measure for which data are collected, by arm or comparison group and by category (if specified).

(v) *Statistical Analyses.* Result(s) of scientifically appropriate tests of the statistical significance of the primary and secondary outcome measures, if any.

(A) A statistical analysis is required to be submitted if it is:

(*1*) Pre-specified in the protocol and/or statistical analysis plan and was performed on the outcome measure data,

(*2*) Made public by the sponsor or responsible party prior to the date on which clinical trial results information is submitted for the primary outcome measures(s) studied in the clinical trial to which the statistical analysis applies, or

(*3*) Conducted on a primary outcome measure in response to a request made by FDA prior to the date on which clinical trial results information is submitted for the primary outcome measure(s) studied in the clinical trial to which the statistical analysis applies.

(B) Information for each statistical analysis specified in paragraph (a)(3)(v)(A) of this section must include the following elements:

(*1*) *Statistical Analysis Overview:* Identification of the arms or comparison groups compared in the statistical analysis; the type of statistical test conducted; and, for a non-inferiority or equivalence test, a description of the analysis that includes, at minimum, the power calculation and non-inferiority or equivalence margin.

(*2*) One of the following, as applicable:

(*i*) *Statistical Test of Hypothesis:* The p-value and the procedure used for the statistical analysis; or

(*ii) Method of Estimation:* The estimation parameter, estimated value, and confidence interval (if calculated).

(4) *Adverse event information.* (i) Information to describe the methods for collecting adverse events during an applicable clinical trial:

(A) *Time Frame.* The specific period of time over which adverse event information was collected and for which information is submitted in paragraph (a)(4)(iii) of this section.

(B) *Adverse Event Reporting Description.* If the adverse event information collected in the clinical trial is collected based on a different definition of adverse event and/or serious adverse event than defined in this part, a brief description of how those definitions differ.

(C) *Collection Approach.* The type of approach taken to collect adverse event information, whether systematic or non-systematic.

(ii) Information for completing three tables summarizing anticipated and unanticipated adverse events collected during an applicable clinical trial:

(A) Table of all serious adverse events grouped by organ system, with the number and frequency of each event by arm or comparison group;

(B) Table of all adverse events, other than serious adverse events, that exceed a frequency of 5 percent within any arm of the clinical trial, grouped by organ system, with the number and frequency of each event by arm or comparison group; and

(C) Table of all-cause mortality, with the number and frequency of deaths due to any cause by arm or comparison group.

(iii) Information for each table specified in paragraph (a)(4)(ii) of this section must include the following elements, unless otherwise specified:

(A) *Adverse Event Arm/Group Information.* A brief description of each arm or comparison group used for submitting adverse event information from the clinical trial, including a descriptive title used to identify each arm or comparison group.

(B) *Total Number Affected.* The overall number of human subjects affected, by arm or comparison group, by:

(*1*) Serious adverse event(s);

(*2*) Adverse event(s) other than serious adverse events that exceed a frequency of 5 percent within any arm of the clinical trial; and

(*3*) Deaths due to any cause.

(C) *Total Number at Risk.* The overall number of human subjects included in the assessment, by arm or comparison group, for:

(*1*) Serious adverse events;

(*2*) Adverse event(s) other than serious adverse events that exceed a frequency of 5 percent within any arm of the clinical trial; or

(*3*) Deaths due to any cause.

(D) *Adverse Event Information.* For the two tables described in paragraphs (a)(4)(ii)(A) and (B) of this section, a description of each type of serious adverse event and other adverse event that is not a serious adverse event and exceeds a frequency of 5 percent within any arm of the clinical trial, consisting of the following attributes:

(*1*) Descriptive term for the adverse event; and

(*2*) Organ system associated with the adverse event.

(E) *Adverse Event Data.* For the two tables described in paragraphs (a)(4)(ii)(A) and (B) of this section and for each adverse event listed in accordance with paragraph (a)(4)(iii)(D) of this section:

(*1*) Number of human subjects affected by such adverse event.

(*2)* Number of human subjects at risk for such adverse event.

(5) *Protocol and statistical analysis plan.* A copy of the protocol and the statistical analysis plan (if not included in the protocol), including all amendments that have been approved by a human subjects protection review board (if applicable) before the time of submission under this subsection and that apply to all clinical trial Facility Locations. The responsible party must include the Official Title (as defined in § 11.10(b)(2)), NCT number (as defined in § 11.10(a)) (if available), and date of the protocol and the statistical analysis plan on the cover page of each document. The responsible party may redact names, addresses, and other personally identifiable information, as well as any trade secret and/or confidential commercial information (as those terms are defined in the Freedom of Information Act (5 U.S.C. 552) and the Trade Secrets Act (18 U.S.C. 1905)) contained in the protocol or statistical analysis plan prior to submission, unless such information is otherwise required to be submitted under this part. The protocol and statistical analysis plan must be submitted in a common electronic document format specified at *https://prsinfo.clinicaltrials.gov.*

(6) *Administrative information*—(i) *Results Point of Contact.* Point of contact for scientific information about the clinical trial results information, including the following:

(A) Name or official title of the point of contact

(B) Name of the affiliated organization, and

(C) Telephone number and email address of the point of contact.

(ii) Certain Agreements. An indication of whether the principal investigator is an employee of the sponsor and, if not, whether there exists any agreement (other than an agreement solely to comply with applicable provisions of law protecting the privacy of human subjects participating in the clinical trial) between the sponsor or its agent and the principal investigator that restricts in any manner the ability of the principal investigator, after the primary completion date of the clinical trial, to discuss the results of the clinical trial at a scientific meeting or any other public or private forum or to publish in a scientific or academic journal information concerning the results of the clinical trial

(7) *Additional clinical trial results information for applicable device clinical trials of unapproved or uncleared device products.* (i) For an applicable device clinical trial of an unapproved or uncleared device product and for which clinical trial registration information has not been posted publicly on Clinical Trials.gov by the Director in accordance with § 11.35(b)(2)(i), the responsible party must provide the following data elements, as the data elements are defined in § 11.10(b): Brief Title; Official Title; Brief Summary; Primary Purpose; Study Design; Study Type; Primary Disease or Condition Being Studied in the Trial, or the Focus of the Study; Intervention Name(s); Other Intervention Name(s); Intervention Description; Intervention Type; Device Product Not Approved or Cleared by U.S. FDA, if any studied intervention is a device product; Study Start Date; Primary Completion Date; Study Completion Date, Enrollment; Primary Outcome Measure Information; Secondary Outcome Measure Information; Eligibility Criteria; Sex/Gender; Age Limits; Accepts Healthy Volunteers; Overall Recruitment Status; Why Study Stopped; Name of the Sponsor; Responsible Party, by Official Title; Facility Name and Facility Location, for each participating facility in a clinical trial; Unique Protocol Identification Number; Secondary ID; Human Subjects Protection Review Board Status; and Record Verification Date.

(ii) The responsible party shall submit all the results information specified in paragraph (a)(7)(i) and must submit an affirmation that any information previously submitted to *ClinicalTrials.gov* for the data elements listed in paragraph (a)(7)(i) of this section have been updated in accordance with § 11.64(a) and are to be included as clinical trial results information.

(b) *Pediatric postmarket surveillance of a device product that is not a clinical trial.* For each pediatric postmarket surveillance of a device product that is not a clinical trial, the responsible party must submit a copy of any final report that is submitted to FDA as specified in 21 CFR 822.38. The responsible party may redact names, addresses, and other personally identifiable information or commercial confidential information contained in the final report prior to submission to NIH, unless such information is otherwise required to be submitted under this part. The final report must be in a common electronic document format specified at *https://prsinfo.clinicaltrials.gov.*

§ 11.52 By when will the NIH Director post submitted clinical trial results information?

Except for clinical trial results information submitted under section 402(j)(4)(A) of the PHS Act and § 11.60, the Director will post publicly clinical trial results information on *ClinicalTrials.gov* not later than 30 calendar days after the date of submission.

§ 11.54 What are the procedures for requesting and obtaining a waiver of the requirements for clinical trial results information submission?

(a) *Waiver request.* (1) A responsible party for an applicable clinical trial with a primary completion date on or after January 18, 2017 may request a waiver from any applicable requirement(s) of this subpart C by submitting a waiver request in the format specified at *https://prsinfo.clinicaltrials.gov/* to the Secretary or delegate prior to the deadline specified in § 11.44(a) for submitting clinical trial results information.

(2) The waiver request must contain:

(i) The NCT number, Brief Title, and Name of the Sponsor of the applicable clinical trial for which the waiver is requested;

(ii) The specific requirement(s) of this subpart C for which the waiver is requested; and

(iii) A description of the extraordinary circumstances that the responsible party believes justify the waiver and an explanation of why granting the request would be consistent with the protection of public health or in the interest of national security.

(3) The responsible party will not be required to comply with the specified requirements of this subpart for which a waiver is granted.

(4) The responsible party must comply with any requirements of this subpart for which a waiver is not granted or must submit an appeal as set forth in paragraph (b) of this section. The deadline for submitting any required clinical trial results information will be the later of the original submission deadline or 30 calendar days after the notification of the denial is sent to the responsible party.

(b) *Appealing a denied waiver request.* (1) A responsible party for an applicable clinical trial with a primary completion date on or after January 18,

2017 may appeal a denied waiver request by submitting an appeal to the Secretary or delegate in the format specified at *https://prsinfo.clinicaltrials.gov/* not later than 30 calendar days after the date on which the electronic notification of the denial in paragraph (a)(4) of this section denying the request is sent to the responsible party.

(2) The responsible party is not required to comply with any requirements of this subpart for which a waiver is granted upon appeal.

(3) The responsible party must submit clinical trial results information to comply with any requirements of this subpart that are not waived upon appeal by the later of the original submission deadline or 30 calendar days after the notice of the denial upon appeal is sent to the responsible party.

(c) If a waiver is granted under paragraph (a) or (b) of this section:

(1) The Director will include a notation in the clinical trial record that specified elements of the requirements of this part have been waived.

(2) The Secretary will notify, in writing, the appropriate committees of Congress and provide an explanation for why the waiver was granted, not later than 30 calendar days after any waiver is granted.

(d) A responsible party for an applicable clinical trial with a primary completion date before January 18, 2017 may request a waiver from any applicable requirement(s) for clinical trial results information submission by submitting a waiver request, as specified in section 402(j)(3)(H) of the Public Health Service Act (42 U.S.C. 282(j)(3)(H)).

Subpart D—Additional Submissions of Clinical Trial Information

§ 11.60 What requirements apply to the voluntary submission of clinical trial information for clinical trials of FDA-regulated drug products (including biological products) and device products?

(a) If a responsible party voluntarily submits clinical trial information for a clinical trial described in paragraph (a)(1) of this section, the responsible party must meet the conditions specified in paragraph (a)(2) of this section.

(1) The requirements of paragraph (a) of this section apply to a clinical trial that was initiated before January 18, 2017 and has a primary completion date before January 18, 2017, and that is either:

(i) A clinical trial of an FDA-regulated drug product (including a biological product) or device product that is not an applicable clinical trial, or

(ii) An applicable clinical trial that is not otherwise required to submit clinical trial registration information.

(2) If the responsible party for a clinical trial described in paragraph (a)(1) of this section voluntarily submits clinical trial registration information and/or clinical trial results information, the responsible party must comply with the following requirements:

(i) The responsible party must submit the information in paragraphs (b)(2)(i)(A), (B), or (C) of this section for the clinical trial being submitted voluntarily.

(A) If the responsible party voluntarily registers a clinical trial, the responsible party must submit clinical trial registration information specified in section 402(j)(2)(A)(ii) of the Public Health Service Act (42 U.S.C. 282(j)(2)(A)(ii)).

(B) If the responsible party voluntarily submits clinical trial results information for a clinical trial for which the clinical trial registration information specified in section 402(j)(2)(A)(ii) of the Public Health Service Act (42 U.S.C. 282(j)(2)(A)(ii)) has not been submitted, the responsible party must submit the clinical trial results information specified in sections 402(j)(3)(C) and 402(j)(3)(I) of the Public Health Service Act (42 U.S.C. 282(j)(3)(C) and 42 U.S.C. 282(j)(3)(I)).

(C) If the responsible party both voluntarily submits clinical trial registration information and voluntarily submits clinical trial results information, the responsible party must submit both clinical trial registration information specified in section 402(j)(2)(A)(ii) of the Public Health Service Act (42 U.S.C. 282(j)(2)(A)(ii)) and clinical trial results information specified in sections 402(j)(3)(C) and 402(j)(3)(I) of the Public Health Service Act (42 U.S.C. 282(j)(3)(C) and 42 U.S.C. 282(j)(3)(I)).

(ii) If, on or after September 27, 2007, a manufacturer submits an application or premarket notification to FDA for approval, licensure, or clearance of a drug product (including a biological product) or device product under sections 505, 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C 355, 360(k), 360e, 360j(m)) or section 351 of the Public Health Service Act (42 U.S.C. 262) for the use studied in the clinical trial submitted under paragraph (a)(1) of this section, the responsible party specified in paragraph (a)(1) of this section must also submit the information specified in paragraph (a)(2)(iii) of this section by the deadline specified in paragraph (a)(2)(iv)(B) of this section for any applicable clinical trial that has not been submitted to *ClinicalTrials.gov* and that meets the following criteria:

(A) The applicable clinical trial is required to be submitted to FDA under sections 505, 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355, 360(k), 360e, 360j(m)) or section 351 of the Public Health Service Act (42 U.S.C. 262) in an application or premarket notification for approval, licensure, or clearance to market the drug product (including a biological product) or device product for the use studied in the clinical trial specified in paragraph (a)(1) of this section; and

(B) The manufacturer of the drug product (including a biological product) or device product studied in the applicable clinical trial is also the responsible party for the clinical trial specified in paragraph (a)(1) of this section.

(iii) Information to be submitted for clinical trials described in paragraph (a)(2)(ii) of this section:

(A) If the clinical trial information voluntarily submitted for a clinical trial described in paragraph (a)(1) of this section consists only of the clinical trial registration information specified in section 402(j)(2)(A)(ii) of the Public Health Service Act (42 U.S.C. 282(j)(2)(A)(ii)), the information to be submitted in accordance with paragraph (a)(2)(ii) of this section must consist, at minimum, of the clinical trial registration information specified in section 402(j)(2)(A)(ii) of the Public Health Service Act (42 U.S.C. 282(j)(2)(A)(ii)).

(B) If the clinical trial information voluntarily submitted for a clinical trial described by paragraph (a)(1) of this section consists of the clinical trial results information specified in sections 402(j)(3)(C) and 402(j)(3)(I) of the Public Health Service Act (42 U.S.C. 282(j)(3)(C) and 42 U.S.C. 282(j)(3)(I)), the information to be submitted in accordance with paragraph (a)(2)(ii) of this section must consist of the clinical trial results information specified in sections 402(j)(3)(C) and 402(j)(3)(I) of the Public Health Service Act (42 U.S.C. 282(j)(3)(C) and 42 U.S.C. 282(j)(3)(I)).

(C) If the clinical trial information voluntarily submitted for a clinical trial described by paragraph (a)(1) of this section consists of both the clinical trial registration information specified in section 402(j)(2)(A)(ii) of the Public Health Service Act (42 U.S.C. 282(j)(2)(A)(ii)) and the clinical trial results information specified in sections 402(j)(3)(C) and 402(j)(3)(I) of the Public Health Service Act (42 U.S.C. 282(j)(3)(C) and 42 U.S.C. 282(j)(3)(I)), the information to be submitted in

accordance with paragraph (a)(2)(ii) of this section must consist of both the clinical trial registration information specified in section 402(j)(2)(A)(ii) of the Public Health Service Act (42 U.S.C. 282(j)(2)(A)(ii)) and the clinical trial results information specified in sections 402(j)(3)(C) and 402(j)(3)(I) of the Public Health Service Act (42 U.S.C. 282(j)(3)(C) and 42 U.S.C. 282(j)(3)(I)).

(iv) Submission deadlines:

(A) Secondary outcome measure(s) and adverse event information for voluntarily submitted clinical trials, under paragraph (a) of this section:

(*1*) If data collection for secondary outcome measure(s) for a voluntarily submitted clinical trial under paragraph (a) of this section is not completed by the primary completion date of the voluntarily submitted clinical trial, clinical trial results information for the secondary outcome measure(s) required in section 402(j)(3)(C) of the Public Health Service Act (42 U.S.C. 282(j)(3)(C)) must be submitted by the later of the date that the clinical trial results information is voluntarily submitted for the primary outcome measure(s) or 1 year after the date on which the final subject was examined or received an intervention for the purposes of final collection of data for the secondary outcome(s), whether the clinical trial was concluded according to the pre-specified protocol or was terminated.

(*2*) If data collection for adverse event information continues after the primary completion date of the voluntarily submitted clinical trial, any adverse event information collected after the primary completion date and subject to the submission requirements in section 402(j)(3)(I) of the Public Health Service Act (42 U.S.C. 282(j)(3)(I)) must be submitted by the later of the date that the clinical trial results information is voluntarily submitted for the primary outcome measure(s) or 1 year after the date of final collection of data for adverse event information, whether the clinical trial was concluded according to the pre-specified protocol or was terminated.

(B) The clinical trial information specified in paragraph (a)(2)(iii) of this section must be submitted not later than the later of the date on which the application or premarket notification to FDA for approval, licensure, or clearance to market a drug product (including a biological product) or device product under section 351 of the Public Health Service Act (42 U.S.C. 262) or section 505, 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355, 360(k), 360e, 360j(m)) for the use studied in the clinical trial specified under paragraph (a)(1) of this section is submitted to FDA or the date on which the clinical trial information specified in paragraph (a)(2)(i) of this section for the clinical trial specified under paragraph (a)(1) of this section is submitted to *ClinicalTrials.gov*.

(b) If a responsible party voluntarily submits clinical trial information for a clinical trial described in paragraph (b)(1) of this section, the responsible party must meet the conditions specified in paragraph (b)(2) of this section.

(1) The requirements of paragraph (b) of this section apply to a clinical trial that was initiated before January 18, 2017 and has a primary completion date on or after January 18, 2017, and that is either:

(i) A clinical trial of an FDA-regulated drug product (including a biological product) or device product that is not an applicable clinical trial; or

(ii) An applicable clinical trial that is not otherwise required to submit clinical trial registration information.

(2) If the responsible party for a clinical trial described in paragraph (b)(1) of this section voluntarily submits clinical trial registration information and/or clinical trial results information, the responsible party must comply with the following requirements:

(i) The responsible party must submit the information in paragraph (b)(2)(i)(A), (B), or (C) of this section for the clinical trial being submitted voluntarily.

(A) If the responsible party voluntarily registers a clinical trial, the responsible party must submit clinical trial registration information specified in section 402(j)(2)(A)(ii) of the Public Health Service Act (42 U.S.C. 282(j)(2)(A)(ii)).

(B) If the responsible party voluntarily submits clinical trial results information for a clinical trial for which the clinical trial registration information specified in section 402(j)(2)(A)(ii) of the Public Health Service Act (42 U.S.C. 282(j)(2)(A)(ii)) has not been submitted, the responsible party must submit the data elements specified in § 11.48, as well as the data elements listed below, as those data elements are defined in § 11.10(b) and apply to the clinical trial and the intervention(s) studied: Brief Title; Official Title; Brief Summary; Primary Purpose; Study Design; Study Phase, for a clinical trial of a drug product (including a biological product); Study Type; Pediatric Postmarket Surveillance of a Device Product; Primary Disease or Condition Being Studied in the Trial, or the Focus of the Study; Intervention Name(s), for each intervention studied; Other Intervention Name(s), for each intervention studied; Intervention Description, for each intervention studied; Intervention Type, for each intervention studied; Device Product Not Approved or Cleared by U.S. FDA, if any studied intervention is a device product; Product Manufactured in and Exported from the U.S.; Studies a U.S. FDA-regulated Device Product; Studies a U.S. FDA-regulated Drug Product; Study Start Date; Primary Completion Date; Study Completion Date; Enrollment; Eligibility Criteria; Sex/Gender; Age Limits; Accepts Healthy Volunteers; Overall Recruitment Status; Why Study Stopped; Availability of Expanded Access, if any studied intervention is an investigational drug product (including a biological product); Name of the Sponsor; Responsible Party, by Official Title; Facility Information, for each participating facility; Unique Protocol Identification Number; Secondary ID; U.S. Food and Drug Administration IND or IDE Number; Human Subjects Protection Review Board Status; Record Verification Date; and Responsible Party Contact Information.

(C) If the responsible party both voluntarily submits clinical trial registration information and voluntarily submits clinical trial results information, the responsible party must submit both the clinical trial registration information specified in section 402(j)(2)(A)(ii) of the Public Health Service Act (42 U.S.C. 282(j)(2)(A)(ii)) and the clinical trial results information specified in § 11.48.

(ii) If, on or after September 27, 2007, a manufacturer submits an application or premarket notification to FDA for approval, licensure, or clearance of a drug product (including a biological product) or device product under section 505, 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355, 360(k), 360e, 360j(m)) or section 351 of the Public Health Service Act (42 U.S.C. 262) for the use studied in the clinical trial submitted under paragraph (b)(1) of this section, the responsible party specified in paragraph (b)(1) of this section must also submit the information specified in paragraph (b)(2)(iii) of this section by the deadline specified in paragraph (b)(2)(iv)(B) of this section for any applicable clinical trial that has not been submitted to *ClinicalTrials.gov* and that meets the following criteria:

(A) The applicable clinical trial is required to be submitted to FDA under section 505, 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355, 360(k), 360e,

360j(m)) or section 351 of the Public Health Service Act (42 U.S.C. 262) in an application or premarket notification for approval, licensure, or clearance to market the drug product (including a biological product) or device product for the use studied in the clinical trial specified in paragraph (b)(1) of this section; and

(B) The manufacturer of the drug product (including a biological product) or device product studied in the applicable clinical trial is also the responsible party for the clinical trial specified in paragraph (b)(1) of this section.

(iii) Information to be submitted for clinical trials described in paragraph (b)(2)(ii) of this section:

(A) If the clinical trial information voluntarily submitted for a clinical trial described in paragraph (b)(1) of this section consists only of the clinical trial registration information specified in section 402(j)(2)(A)(ii) of the Public Health Service Act (42 U.S.C. 282(j)(2)(A)(ii)), the information to be submitted in accordance with paragraph (b)(2)(ii) of this section must consist, at minimum, of the clinical trial registration information specified in section 402(j)(2)(A)(ii) of the Public Health Service Act (42 U.S.C. 282(j)(2)(A)(ii)).

(B) If the clinical trial information voluntarily submitted for a clinical trial described by paragraph (b)(1) of this section consists of the clinical trial results information specified in § 11.60(b)(2)(i)(B), the information to be submitted in accordance with paragraph (b)(2)(ii) of this section must consist of the clinical trial results information specified in § 11.60(b)(2)(i)(B).

(C) If the clinical trial information voluntarily submitted for a clinical trial described by paragraph (b)(1) of this section consists of both the clinical trial registration information specified in section 402(j)(2)(A)(ii) of the Public Health Service Act (42 U.S.C. 282(j)(2)(A)(ii)) and the clinical trial results information specified in § 11.48, the information to be submitted in accordance with paragraph (b)(2)(ii) of this section must consist of both the clinical trial registration information specified in section 402(j)(2)(A)(ii) of the Public Health Service Act (42 U.S.C. 282(j)(2)(A)(ii)) and the clinical trial results information specified in § 11.48.

(iv) Submission deadlines:

(A) Secondary outcome measure(s) and adverse event information for voluntarily submitted clinical trials, under paragraph (b) of this section:

(*1*) If data collection for secondary outcome measure(s) for a voluntarily submitted clinical trial under paragraph (b) of this section is not completed by the primary completion date of the voluntarily submitted clinical trial, clinical trial results information for the secondary outcome measure(s) required in § 11.48(a)(3) must be submitted by the later of the date that the clinical trial results information is voluntarily submitted for the primary outcome measure(s) or 1 year after the date on which the final subject was examined or received an intervention for the purposes of final collection of data for the secondary outcome(s), whether the clinical trial was concluded according to the pre-specified protocol or was terminated.

(*2*) If data collection for adverse event information continues after the primary completion date of the voluntarily submitted clinical trial, any adverse event information collected after the primary completion date and subject to the submission requirements in § 11.48(a)(4) must be submitted by the later of the date that the clinical trial results information is voluntarily submitted for the primary outcome measure(s) or 1 year after the date of final collection of data for adverse event information, whether the clinical trial was concluded according to the pre-specified protocol or was terminated.

(B) The clinical trial information specified in paragraph (b)(2)(iii) of this section must be submitted not later than the later of the date on which the application or premarket notification to FDA for approval, licensure, or clearance to market a drug product (including a biological product) or device product under section 351 of the Public Health Service Act (42 U.S.C. 262) or section 505, 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355, 360(k), 360e, 360j(m)) for the use studied in the clinical trial specified under paragraph (b)(1) of this section is submitted to FDA or the date on which the clinical trial information specified in paragraph (b)(2)(i) of this section for the clinical trial specified under paragraph (b)(1) of this section is submitted to *ClinicalTrials.gov*.

(c) If a responsible party voluntarily submits clinical trial information for a clinical trial described in paragraph (c)(1) of this section, the responsible party must meet the conditions specified in paragraph (c)(2) of this section.

(1) The requirements of paragraph (c) of this section apply to a clinical trial that was initiated on or after January 18, 2017 and has a primary completion date on or after January 18, 2017, and that is either:

(i) A clinical trial of an FDA-regulated drug product (including a biological product) or device product that is not an applicable clinical trial; or

(ii) An applicable clinical trial that is not otherwise required to submit clinical trial registration information.

(2) If the responsible party for a clinical trial described in paragraph (c)(1) of this section voluntarily submits clinical trial registration information and/or clinical trial results information, the responsible party must comply with the following requirements:

(i) The responsible party must submit the information in paragraph (c)(2)(i)(A), (B), or (C) of this section for the clinical trial being submitted voluntarily.

(A) If the responsible party voluntarily registers a clinical trial, the responsible party must submit the clinical trial registration information specified in § 11.28(a).

(B) If the responsible party voluntarily submits clinical trial results information for a clinical trial for which the clinical trial registration information specified in § 11.28(a) has not been submitted, the responsible party must submit the data elements specified in paragraph (b)(2)(i)(B) of this section.

(C) If the responsible party both voluntarily submits clinical trial registration information and voluntarily submits clinical trial results information, the responsible party must submit both the clinical trial registration information specified in § 11.28(a) and the clinical trial results information specified in § 11.48.

(ii) If, on or after September 27, 2007, a manufacturer submits an application or premarket notification to FDA for approval, licensure, or clearance of a drug product (including a biological product) or device product under section 505, 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355, 360(k), 360e, 360j(m)) or section 351 of the Public Health Service Act (42 U.S.C. 262) for the use studied in the clinical trial submitted under paragraph (c)(1) of this section, the responsible party specified in paragraph (c)(1) of this section must also submit the information specified in paragraph (c)(2)(iii) of this section by the deadline specified in paragraph (c)(2)(iv)(B) of this section for any applicable clinical trial that has not been submitted to *ClinicalTrials.gov* and that meets the following criteria:

(A) The applicable clinical trial is required to be submitted to FDA under section 505, 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355, 360(k), 360e, 360j(m)) or section 351 of the Public Health Service Act (42 U.S.C. 262) in an

application or premarket notification for approval, licensure, or clearance to market the drug product (including a biological product) or device product for the use studied in the clinical trial specified in paragraph (c)(1) of this section; and

(B) The manufacturer of the drug product (including a biological product) or device product studied in the applicable clinical trial is also the responsible party for the clinical trial specified in paragraph (c)(1) of this section.

(iii) Information to be submitted for clinical trials described in paragraph (c)(2)(ii) of this section:

(A) If the clinical trial information voluntarily submitted for a clinical trial described in paragraph (c)(1) of this section consists only of the clinical trial registration information specified in § 11.28(a), the information to be submitted in accordance with paragraph (c)(2)(ii) of this section must consist, at minimum, of the clinical trial registration information specified in § 11.28(a).

(B) If the clinical trial information voluntarily submitted for a clinical trial described by paragraph (c)(1) of this section consists of the clinical trial results information specified in § 11.60(c)(2)(i)(B), the information to be submitted in accordance with paragraph (c)(2)(ii) of this section must consist of the clinical trial results information specified in § 11.60(c)(2)(i)(B).

(C) If the clinical trial information voluntarily submitted for a clinical trial described by paragraph (c)(1) of this section consists of both the clinical trial registration information specified in § 11.28(a) and the clinical trial results information specified in § 11.48, the information to be submitted in accordance with paragraph (c)(2)(ii) of this section must consist of both the clinical trial registration information specified in § 11.28(a) and the clinical trial results information specified in § 11.48.

(iv) Submission deadlines:

(A) Secondary outcome measure(s) and adverse event information for voluntarily-submitted clinical trials, under paragraph (c) of this section:

(*1*) If data collection for secondary outcome measure(s) for a voluntarily submitted clinical trial under paragraph (c) of this section is not completed by the primary completion date of the voluntarily submitted clinical trial, clinical trial results information for the secondary outcome measure(s) required in § 11.48(a)(3) must be submitted by the later of the date that the clinical trial results information is voluntarily submitted for the primary outcome measure(s) or 1 year after the date on which the final subject was examined or received an intervention for the purposes of final collection of data for the secondary outcome(s), whether the clinical trial was concluded according to the pre-specified protocol or was terminated.

(*2*) If data collection for adverse event information continues after the primary completion date of the voluntarily submitted clinical trial, any adverse event information collected after the primary completion date and subject to the submission requirements in § 11.48(a)(4) must be submitted by the later of the date that the clinical trial results information is voluntarily submitted for the primary outcome measure(s) or 1 year after the date of final collection of data for adverse events information, whether the clinical trial was concluded according to the pre-specified protocol or was terminated.

(B) The clinical trial information specified in paragraph (c)(2)(iii) of this section must be submitted not later than the later of the date on which the application or premarket notification to FDA for approval, licensure, or clearance to market a drug product (including a biological product) or device product under section 351 of the Public Health Service Act (42 U.S.C. 262) or section 505, 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355, 360(k), 360e, 360j(m)) for the use studied in the clinical trial specified under paragraph (c)(1) of this section is submitted to FDA or the date on which the clinical trial information specified in paragraph (c)(2)(i) of this section for the clinical trial specified under paragraph (c)(1) of this section is submitted to *ClinicalTrials.gov*.

(v) All submissions of clinical trial information under paragraph (c) of this section are subject to the applicable update and corrections requirements specified in § 11.64.

(d) Statement to accompany applicable clinical trials submitted under paragraphs (a), (b), and (c) of this section. Each applicable clinical trial for which clinical trial information is submitted under paragraphs (a), (b), and (c) of this section and posted on *ClinicalTrials.gov* will include the statement ''This clinical trial information was submitted voluntarily under the applicable law and, therefore, certain submission deadlines may not apply. (That is, clinical trial information for this applicable clinical trial was submitted under section 402(j)(4)(A) of the Public Health Service Act and 42 CFR 11.60 and is not subject to the deadlines established by sections 402(j)(2) and (3) of the Public Health Service Act or 42 CFR 11.24 and 11.44.)''

§ 11.62 What requirements apply to applicable clinical trials for which submission of clinical trial information has been determined by the Director to be necessary to protect the public health?

(a) A responsible party who receives notification that the Director has determined that posting of clinical trial information for an applicable clinical trial described in paragraph (b) of this section is necessary to protect the public health must submit clinical trial information as specified in paragraph (c) of this section.

(b) An applicable clinical trial subject to this section must be either:

(1) An applicable clinical trial of an approved, licensed, or cleared drug product (including a biological product) or device product that has a primary completion date on or after September 27, 1997; or

(2) An applicable clinical trial that is subject to registration under § 11.22(a) and studies a drug product (including a biological product) or device product that is unapproved, unlicensed, or uncleared, regardless of whether approval, licensure, or clearance was, is, or will be sought, and that is not otherwise subject to results information submission in accordance with the regulation.

(c) Deadline for submission of clinical trial information:

(1) *General.* Except as provided in paragraphs (c)(2) and (c)(3) of this section, a responsible party for an applicable clinical trial that is subject to this section must submit the clinical trial registration information specified in § 11.28(a) and the clinical trial results information specified in § 11.48(a) not later than 30 calendar days after the submission date specified in the notification described in paragraph (a) of this section.

(2) *Exception.* If a responsible party submits a certification consistent with § 11.44(b) or (c) not later than 30 calendar days after the submission date specified in the notification described in paragraph (a) of this section, the responsible party must submit the clinical trial results information specified in § 11.48(a) not later than the deadline specified in § 11.44(b) or (c), as applicable.

(3) If a responsible party submitted clinical trial registration information describing the applicable clinical trial specified in the notification described in paragraph (a) of this section prior to the date on which the notification is sent to

the responsible party, the responsible party must update such clinical trial information to reflect changes, if any, in the applicable clinical trial not later than 30 calendar days after the submission date specified in the notification described in paragraph (a) of this section, irrespective of the deadline for updates specified in § 11.64.

§ 11.64 When must clinical trial information submitted to ClinicalTrials.gov be updated or corrected?

(a) *Updates.* (1) Clinical trial registration information:

(i) The responsible party for an applicable clinical trial for which clinical trial registration information was required to be submitted if the clinical trial was initiated before January 18, 2017, must submit updates in accordance with the following:

(A) In general, changes to the clinical trial registration information specified in section 402(j)(2)(A)(ii) of the Public Health Service Act (42 U.S.C. 282(j)(2)(A)(ii)) that was required at the time of submission must be updated not less than once every 12 months.

(B) Overall Recruitment Status must be updated not later than 30 calendar days after any change in overall recruitment status.

(C) Primary Completion Date must be updated not later than 30 calendar days after the clinical trial reaches its actual primary completion date.

(ii) The responsible party for an applicable clinical trial, or for another clinical trial for which registration information was voluntarily submitted pursuant to § 11.60(c), if the clinical trial was initiated on or after January 18, 2017, must submit updates in accordance with the following:

(A) In general, changes to clinical trial registration information specified in § 11.28 must be updated not less than once every 12 months.

(B) If the first human subject was not enrolled in the clinical trial at the time of registration, the Study Start Date data element must be updated not later than 30 calendar days after the first human subject is enrolled.

(C) Intervention Name(s) must be updated to a non-proprietary name not later than 30 calendar days after a non-proprietary name is established for any intervention included in the Intervention Name(s) data element.

(D) Availability of expanded access:

(*1*) If expanded access to an investigational drug product (including a biological product) becomes available after an applicable clinical trial of that product has been registered, the responsible party, if both the manufacturer of the investigational drug product (including a biological product) and the sponsor of the applicable clinical trial, must, not later than 30 calendar days after expanded access becomes available, update the Availability of Expanded Access data element for that applicable clinical trial and, unless an expanded access record has already been created as required by § 11.28(a)(2)(ii)(H), submit the data elements in accordance with § 11.28(c) to create an expanded access record.

(*2*) No later than 30 calendar days after the date on which the responsible party receives an NCT number for an expanded access record created as required by § 11.28(a)(2)(ii)(H), the responsible party must update the Availability of Expanded Access data element by entering the NCT number in the clinical trial record for the applicable clinical trial.

(E) Expanded access record:

(*1*) Expanded Access Status, under § 11.28(c)(2)(iv), must be updated not later than 30 calendar days after a change in the availability of expanded access to an investigational drug product (including a biological product) under section 561 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bbb).

(*2*) Expanded Access Type, under § 11.28(c)(1)(x), must be updated not later than 30 calendar days after a change in the type(s) of expanded access available for an investigational drug product (including a biological product) under section 561 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bbb).

(F) Overall Recruitment Status must be updated not later than 30 calendar days after any change in overall recruitment status. If, at any time, Overall Recruitment Status is changed to ''suspended,'' ''terminated,'' or ''withdrawn,'' the responsible party must also submit the Why Study Stopped data element.

(G) Individual Site Status must be updated not later than 30 calendar days after a change in status for any individual site.

(H) Human Subjects Protection Review Board Status must be updated not later than 30 calendar days after a change in status.

(I) Primary Completion Date must be updated not later than 30 calendar days after the clinical trial reaches its actual primary completion date. At the time, the date is changed to ''actual,'' and the Enrollment data element specifying the actual number of participants enrolled must be submitted.

(J) Study Completion Date must be updated not later than 30 calendar days after the clinical trial reaches its actual study completion date.

(K) Responsible Party, by Official Title must be updated not later than 30 calendar days after a change in the responsible party or the official title of the responsible party.

(L) Responsible Party Contact Information must be updated not later than 30 calendar days after a change in the responsible party or the contact information for the responsible party.

(M) Device Product Not Approved or Cleared by U.S. FDA must be updated not later than 15 calendar days after a change in approval or clearance status has occurred.

(N) Record Verification Date must be updated any time the responsible party reviews the complete set of submitted clinical trial information for accuracy and not less than every 12 months, even if no other updated information is submitted at that time.

(O) If a protocol is amended in such a manner that changes are communicated to human subjects in the clinical trial, updates to any relevant clinical trial registration information data elements must be submitted not later than 30 calendar days after the protocol amendment is approved by a human subjects protection review board.

(iii) In addition to the update requirements established in paragraphs (a)(1)(i) and (a)(1)(ii) of this section, clinical trial registration information must be updated at the time that clinical trial results information for that clinical trial is initially submitted.

(A) If the clinical trial was initiated before January 18, 2017, a responsible party must submit updates to the clinical trial registration information described in § 11.64(a)(1)(i).

(B) If the clinical trial was initiated on or after January 18, 2017, the responsible party must submit updates to the clinical trial registration information in accordance with § 11.64(a)(1)(ii).

(2) *Clinical trial results information.* The responsible party for an applicable clinical trial, or for another clinical trial for which results information was voluntarily submitted pursuant to § 11.60(b) or (c), where the clinical trial has a Primary Completion Date on or after January 18, 2017, must submit updates in accordance with the following:

(i) In general, changes to required clinical trial results information, other than the protocol and statistical analysis plan specified in § 11.48(a)(5) and certain agreements specified in § 11.48(a)(6)(ii),must be updated not less than once every 12 months.

(ii) For applicable device clinical trials of unapproved or uncleared device products, the responsible party must update the following data elements, as defined in § 11.10(b), in accordance with the following:

(A) Intervention Name(s) must be updated to a non-proprietary name not later than 30 calendar days after a non-proprietary name is established for any intervention included in the Intervention Name(s) data element.

(B) Primary Completion Date must be updated not later than 30 calendar days after the clinical trial reaches its actual primary completion date. At the time the date is changed to ''actual,'' the Enrollment data element specifying the actual number of participants enrolled must be submitted.

(C) Study Completion Date must be updated not later than 30 calendar days after the clinical trial reaches its actual study completion date.

(D) Overall Recruitment Status must be updated not later than 30 calendar days after any change in overall recruitment status. If, at any time, Overall Recruitment Status is changed to ''suspended,'' ''terminated,'' or ''withdrawn,'' the responsible party must also submit the Why Study Stopped data element.

(E) Record Verification Date must be updated any time the responsible party reviews the complete set of submitted clinical trial information for accuracy and not less than every 12 months, even if no other updated information is submitted at that time.

(3) A responsible party's obligation to submit updates as specified in this section ends on the date on which all required clinical trial results information has been submitted as specified in sections 402(j)(3)(C) and 402(j)(3)(I) of the Public Health Service Act (42 U.S.C. 282(j)(3)(C)) and 42 U.S.C. 282(j)(3)(I)) or as specified in § 11.48, as applicable, and corrections have been made or addressed in response to any electronic notice received under § 11.64(b)(1). If no clinical trial results information is required to be submitted, a responsible party's obligation to submit updates to clinical trial registration information ends on the date on which all required clinical trial registration information has been submitted as specified in section 402(j)(2)(A)(ii) of the Public Health Service Act (42 U.S.C. 282(j)(2)(A)(ii) or § 11.28, as applicable, and corrections have been made or addressed in response to any electronic notice received under § 11.64(b)(1).

(4) *Public availability of updates.* (i) Updates to clinical trial registration information and clinical trial results information will be posted in accordance with § 11.35 and § 11.52, respectively.

(ii) The Director will retain prior clinical trial registration information and clinical trial results information and make it publicly available in accordance with § 11.35 and § 11.52, respectively, through *ClinicalTrials.gov* so that updates do not result in the removal of any information from the original submission or any preceding update.

(b) Corrections—(1) *Quality control.* After clinical trial registration information has been submitted as specified in section 402(j)(2)(A)(ii) of the Public Health Service Act (42 U.S.C. 282(j)(2)(A)(ii)) or § 11.28, as applicable, or clinical trial results information has been submitted as specified in sections 402(j)(3)(C) and 402(j)(3)(I) of the Public Health Service Act (42 U.S.C. 282(j)(3)(C) and 42 U.S.C. 282(j)(3)(I)) or § 11.48, as applicable, including the updates specified in paragraph (a) of this section, the Director may provide electronic notification to the responsible party of apparent errors, deficiencies, and/or inconsistencies in the submitted information identified during procedures for quality control review established by the Director, as specified at *https://prsinfo.clinicaltrials.gov.* The responsible party must correct or address all apparent errors, deficiencies, and/or inconsistencies identified in the notification not later than 15 calendar days for clinical trial registration information, or 25 calendar days for clinical trial results information, after the date of the electronic notification sent to the responsible party.

(2) *Other corrections.* (i) A responsible party who becomes aware of errors, other than those specified in paragraph (b)(1) of this section, in any clinical trial information submitted under this part shall have not more than 15 calendar days for clinical trial registration information, or 25 calendar days for clinical trial results information, to correct or address such errors.

(ii) A responsible party's obligation to correct or address errors as specified in paragraph (b)(2) of this section ends on the date on which all required clinical trial results information has been submitted as specified in sections 402(j)(3)(C) and 402(j)(3)(I) of the Public Health Service Act (42 U.S.C. 282(j)(3)(C) and 42 U.S.C. 282(j)(3)(I)) or § 11.48, as applicable, and corrections have been made or addressed in response to any electronic notice received under § 11.64(b)(1). If no clinical trial results information is required to be submitted, a responsible party's obligation to correct or address errors ends on the date on which all required clinical trial registration information has been submitted as specified in section 402(j)(2)(A)(ii) of the Public Health Service Act (42 U.S.C. 282(j)(2)(A)(ii)) or § 11.28, as applicable, and corrections have been made or addressed in response to any electronic notice received under § 11.64(b)(1).

(3) Compliance with the quality control review process, including the requirements of this section, does not constitute a legal defense to enforcement pursuant to section 301(jj) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 331(jj)), section 303(f)(3) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 333(f)(3)), or any other Federal law.

Subpart E—Potential Legal Consequences of Non-compliance

§ 11.66 What are potential legal consequences of not complying with the requirements of this part?

(a) *Civil or criminal judicial actions.* Failure to comply with the requirements of this part, issued under section 402(j) of the Public Health Service Act (42 U.S.C. 282(j)), is a prohibited act under one or more provisions of section 301(jj) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(jj)):

(1) Failure to submit the certification required by section 402(j)(5)(B) of the Public Health Service (42 U.S.C. 282(j)(5)(B)) that all applicable requirements of section 402(j) have been met, or knowingly submitting a false certification under section 402(j)(5)(B), is a prohibited act under section 301(jj)(1) of the Federal Food, Drug, and Cosmetic Act.

(2) Failure to submit clinical trial information required under section 402(j) of the Public Health Service Act is a prohibited act under section 301(jj)(2) of the Federal Food, Drug, and Cosmetic Act.

(3) Submission of clinical trial information under section 402(j) that is false or misleading in any particular is a prohibited act under section 301(jj)(3) of the Federal Food, Drug, and Cosmetic Act.

(b) *Civil monetary penalty actions.* Any person who violates section 301(jj) of the Federal Food, Drug, and Cosmetic Act is subject to civil monetary penalties under section 303(f)(3) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 333(f)(3)).

(c) *Grant funding actions.* Under section 402(j)(5)(A) of the Public Health Service Act (42 U.S.C. 282(j)(5)(A)), if an applicable clinical trial is funded in whole or part by the Department of Health and Human Services, any required grant or progress report forms

must include a certification that the responsible party has made all required registration and results submissions. If it is not verified that the required registration and results clinical trial information for each applicable clinical trial for which a grantee is the responsible party has been submitted, any remaining funding for a grant or funding for a future grant to such grantee will not be released. If the head of an HHS agency verifies that a grantee has not submitted such required clinical trial information, the agency head will provide notice to the grantee of the non-compliance and allow the grantee 30 days to correct the non-compliance and submit the required clinical trial information.

Dated: September 8, 2016.

Francis S. Collins,

Director, National Institutes of Health.

Approved: Dated: September 9, 2016.

Sylvia Mathews Burwell,

Secretary.

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